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Kidney transplant graft outcomes in 379 257 recipients on 3 continents

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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 4 countries (United States, United Kingdom, Australia, and New Zealand) on 3 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, 1-year adjusted graft failure risk was significantly higher in the United Kingdom (hazard ratio [HR] 1.22, 95% confidence interval [CI] 1.18-1.26, $P < .001$) and New Zealand (hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.14-1.46, $P < .001$), but lower in Australia (HR 0.90, 95% CI 0.84-0.96, $P = .001$). In contrast, long-term adjusted graft failure risk (conditional on 1-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 $P < .001$). Thus long-term kidney graft outcomes are approximately 25% worse in the United States than in 3 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.

KEYWORDS

clinical research/practice, graft survival, kidney disease, kidney transplantation/nephrology, rejection, Scientific Registry of Transplant Recipients (SRTR)

1 | 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 posttransplantation outcomes to a centralized registry in some countries offers a unique opportunity to explore country-level differences on outcomes. Kim et al showed a 49% higher risk of death beyond the first posttransplantation year in an 8-year cohort of United States kidney transplant recipients compared to a cohort of Canadians transplanted in during the same period.[2] However, the absolute long-term risk of death after kidney transplantation 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

Abbreviations: ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CI, confidence interval; HR, hazard ratio; NHSBT, National Health Service Blood and Transplant for the United Kingdom; SRTR, Scientific Registry of Transplant Recipients.

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 last quarter century in 4 countries on 3 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.

2 | MATERIALS AND METHODS

Patient-level data were combined from 3 transplant registries covering 4 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 3 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 on 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 reported previously.[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 to 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 1 year (short-term) and long-term graft failure. The short-term graft failure model examined the time from transplantation to graft failure (as defined above), censored at the earlier of end of follow-up or 1-year posttransplantation. The long-term graft failure model was conditional on the recipient being alive with graft function at 1 year. Time at risk for the long-term model began at 1-year posttransplantation and continued to graft failure (as defined above), censored at the earlier of end of follow-up or end of study. 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 transplantation. 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 nonproportional hazards in the country effects; country parameter estimates for this model should be interpreted as the average effects over the first posttransplantation 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 2-sided *P*-value ≤ .05 were considered statistically significant.

3 | RESULTS

3.1 | Descriptive statistics

There were 379 257 kidney transplants performed in the 4 countries from 1988 to 2014. Characteristics of the study cohort are shown

in Table 1. Median recipient age at transplantation 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%).

3.2 | One-year and conditional long-term graft failure models

Compared to the United States, the 1-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 $P < .001$) (Figure 1A). The 1-year risk of graft failure in Australia was lower than in the United States (HR 0.90, $P = .001$).

In contrast to the 1-year results, the risk of long-term graft failure (conditional on function at 1 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 $P < .001$) (Figure 1B). Median graft survival times at the overall average covariate values were 11.2 years for the United States, compared to >14.7 years for Australia, New Zealand, and the United Kingdom.

3.3 | 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 the 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 2 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, $P < .001$ Australia vs United States; HR = 0.86, $P < .001$ New Zealand vs United States; HR = 0.90, $P < .001$ United Kingdom vs United States; United States Medicare/Medicaid: HR = 0.63, $P < .001$ Australia vs United States; HR = 0.66, $P < .001$ New Zealand vs United States; HR = 0.65, $P < .001$ United Kingdom vs United States).

3.4 | Time trend in country-specific graft failure risk

The risk of short-term graft failure decreased significantly over the 27-year cohort period (each within-country slope $P < .001$) (Figure 2A). In 1988, 1-year risk was significantly higher in New Zealand and the United Kingdom than in the United States ($P < .001$). Thereafter, a larger decrease in 1-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; $P = .08$), such that the 1-year risk became equal to the United States by 2014. The rate of improvement in 1-year graft failure risk was not significantly different between the United States and Australia. The improvement in 1-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, $P < .001$).

Long-term graft failure risk, conditional on function at 1 year, also improved in all 4 countries over time (each $P < .001$) (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; $P = .03$) (Figure 2B). Long-term outcome remained worse in the United States throughout the period of study.

3.5 | 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

TABLE 1 Characteristics of the study cohort

Characteristic median (Q1,Q3) or n (%)	Australia (n = 13 582)	New Zealand (n = 2471)	United Kingdom (n = 44 781)	United States (n = 318 423)	Total (n = 379 257)
Recipient age (y)	48 (35,57)	46 (32,57)	46 (33,57)	48 (36,59)	48 (35,58)
Recipient sex: male	8318 (61.2%)	1540 (62.3%)	27 746 (62.0%)	192 297 (60.4%)	229 901 (60.6%)
Recipient race					
Asian	1088 (8.0%)	165 (6.7%)	3563 (8.0%)	14 939 (4.7%)	19 755 (5.2%)
White	11 343 (83.5%)	1748 (70.7%)	24 462 (54.6%)	179 142 (56.3%)	216 695 (57.1%)
Other	1111 (8.2%)	555 (22.5%)	2087 (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	1172 (8.6%)	262 (10.6%)	2878 (6.4%)	75 446 (23.7%)	79 758 (21.0%)
Glomerulonephritis	6231 (45.9%)	1105 (44.7%)	7104 (15.9%)	86 588 (27.2%)	101 028 (26.6%)
Other	6179 (45.5%)	1104 (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 (y)	46 (33,56)	41 (28,51)	46 (33,56)	38 (26,49)	40 (26,50)
Donor sex: male	7254 (53.4%)	1255 (50.8%)	23 489 (52.5%)	169 534 (53.2%)	201 532 (53.1%)
Donor type					
Living	4540 (33.4%)	994 (40.2%)	11 060 (24.7%)	115 642 (36.3%)	132 236 (34.9%)
Deceased (brain death)	8224 (60.6%)	1455 (58.9%)	28 325 (63.3%)	188 502 (59.2%)	226 506 (59.7%)
Deceased (circulatory death)	818 (6.0%)	22 (0.9%)	5396 (12.0%)	14 279 (4.5%)	20 515 (5.4%)
Donor cause of death					
Trauma	2910 (21.4%)	537 (21.7%)	7242 (16.2%)	90 852 (28.5%)	101 541 (26.8%)
Nontrauma	5765 (42.4%)	787 (31.8%)	26 327 (58.8%)	111 765 (35.1%)	144 644 (38.1%)
N/A (living donor)	4540 (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	1110 (8.2%)	271 (11.0%)	3019 (6.7%)	35 949 (11.3%)	40 349 (10.6%)
Biologically related nonsibling	1901 (14.0%)	392 (15.9%)	4581 (10.2%)	42 954 (13.5%)	49 828 (13.1%)
Biologically unrelated	1529 (11.3%)	331 (13.4%)	3455 (7.7%)	35 857 (11.3%)	41 172 (10.9%)
N/A (deceased donor)	9042 (66.6%)	1477 (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%)	4191 (9.4%)	28 037 (8.8%)	33 062 (8.7%)
1	1307 (9.6%)	240 (9.7%)	4926 (11.0%)	14 750 (4.6%)	21 223 (5.6%)
2	2990 (22.0%)	572 (23.1%)	11 901 (26.6%)	35 416 (11.1%)	50 879 (13.4%)
3	2893 (21.3%)	620 (25.1%)	13 289 (29.7%)	66 119 (20.8%)	82 921 (21.9%)
4	1963 (14.5%)	466 (18.9%)	6479 (14.5%)	66 991 (21.0%)	75 899 (20.0%)
5	2053 (15.1%)	305 (12.3%)	2729 (6.1%)	69 719 (21.9%)	74 806 (19.7%)
6	1044 (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%)	2747 (0.9%)	3768 (1.0%)

(Continues)

TABLE 1 (Continued)

Characteristic median (Q1,Q3) or n (%)	Australia (n = 13 582)	New Zealand (n = 2471)	United Kingdom (n = 44 781)	United States (n = 318 423)	Total (n = 379 257)
Era of transplant					
1988-1994	2697 (19.9%)	522 (21.1%)	10 032 (22.4%)	59 765 (18.8%)	73 016 (19.3%)
1995-1998	1605 (11.8%)	365 (14.8%)	5624 (12.6%)	40 653 (12.8%)	48 247 (12.7%)
1999-2002	1809 (13.3%)	381 (15.4%)	5475 (12.2%)	47 986 (15.1%)	55 651 (14.7%)
2003-2006	2023 (14.9%)	342 (13.8%)	6071 (13.6%)	55 511 (17.4%)	63 947 (16.9%)
2007-2010	2521 (18.6%)	426 (17.2%)	7950 (17.8%)	57 429 (18.0%)	68 326 (18.0%)
2011-2014	2927 (21.6%)	435 (17.6%)	9629 (21.5%)	57 079 (17.9%)	70 070 (18.5%)

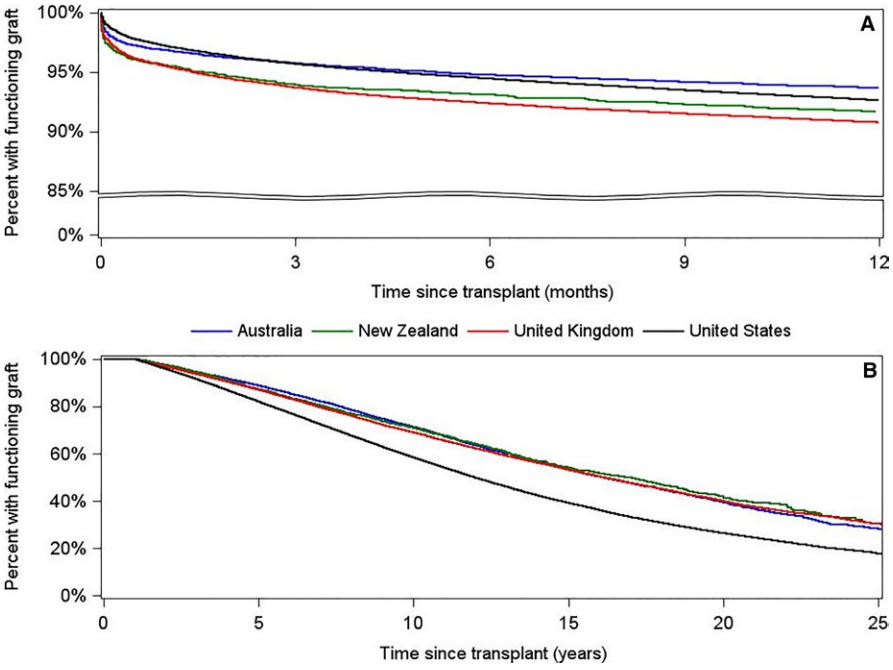

FIGURE 1 Adjusted graft survival by country for (A) 1-year follow-up (n = 379 257, graft failures = 33 981) and (B) long-term follow-up conditional on being alive with a functioning graft at 1 year (n = 318 048, graft failures = 119 322). Survival curves for each country were generated using average 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

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 be explained only by a factor that was at least 31 percentage points more prevalent in the United States than Australia, for example, 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, whereas 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.

4 | 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 3 continents to assess differences in kidney graft outcomes across 4 countries using a uniform analytical methodology. We found that recipients in the United States had a lower risk of graft failure in the first posttransplantation year compared to patients transplanted in the United Kingdom and New Zealand (but not significantly different than Australians). Although 1 year is the traditional short-term milepost for assessing outcome in kidney transplantation, 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 1 year was approximately 25% lower in Australia, New Zealand, and the United Kingdom than in the United States. In patient-centered terms, this represents 3 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

TABLE 2 Adjusted risk of long-term graft failure versus the United States by covariate subcohorts

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**	**<.001**	**<.001**	**<.001**
Recipient age at transplant: <12	8449	1.00	0.73	1.25	**0.79**	.087	1.000	**.029**
Recipient age at transplant: 12 to 17	9882	1.00	0.92	1.14	**0.75**	1.000	1.000	**<.001**
Recipient age at transplant: 18 to 29	35 560	1.00	**0.71**	**0.68**	**0.69**	**<.001**	**<.001**	**<.001**
Recipient age at transplant: 30 to 39	51 608	1.00	**0.70**	0.80	**0.68**	**<.001**	.236	**<.001**
Recipient age at transplant: 40 to 49	70 690	1.00	**0.75**	**0.62**	**0.74**	**<.001**	**<.001**	**<.001**
Recipient age at transplant: 50 to 59	78 217	1.00	**0.80**	0.84	**0.76**	**<.001**	.275	**<.001**
Recipient age at transplant: 60 and over	68 218	1.00	**0.76**	**0.76**	**0.84**	**<.001**	**.035**	**<.001**
Recipient sex: Female	127 274	1.00	**0.76**	**0.70**	**0.74**	**<.001**	**<.001**	**<.001**
Recipient sex: Male	195 350	1.00	**0.73**	**0.79**	**0.74**	**<.001**	**<.001**	**<.001**
Recipient race: Asian	18 439	1.00	0.82	0.94	0.96	.117	1.000	1.000
Recipient race: White	196 372	1.00	**0.73**	**0.73**	**0.74**	**<.001**	**<.001**	**<.001**
Recipient race: Other	107 813	1.00	**1.40**	1.12	**0.56**	**<.001**	1.000	**<.001**
Recipient diagnosis: Diabetes	69 376	1.00	**0.84**	**0.69**	**0.60**	**.014**	**.006**	**<.001**
Recipient diagnosis: Glomerulonephritis	91 244	1.00	**0.79**	**0.82**	**0.83**	**<.001**	**.009**	**<.001**
Recipient diagnosis: Other	162 004	1.00	**0.74**	**0.75**	**0.76**	**<.001**	**<.001**	**<.001**
Donor age: <18	29 822	1.00	**0.79**	0.74	**0.75**	**<.001**	.159	**<.001**
Donor age: 18 to 29	68 956	1.00	**0.74**	**0.75**	**0.74**	**<.001**	**.004**	**<.001**
Donor age: 30 to 39	63 698	1.00	**0.74**	0.83	**0.71**	**<.001**	.519	**<.001**
Donor age: 40 to 49	75 487	1.00	**0.74**	**0.71**	**0.75**	**<.001**	**<.001**	**<.001**
Donor age: 50 to 59	58 519	1.00	**0.76**	**0.73**	**0.71**	**<.001**	**.001**	**<.001**
Donor age: 60 and over	26 142	1.00	**0.74**	0.81	**0.76**	**<.001**	1.000	**<.001**
Donor sex: Female	150 971	1.00	**0.73**	**0.74**	**0.73**	**<.001**	**<.001**	**<.001**
Donor sex: Male	171 653	1.00	**0.75**	**0.76**	**0.74**	**<.001**	**<.001**	**<.001**
Donor type: Living	117 489	1.00	**0.76**	0.87	**0.71**	**<.001**	.613	**<.001**
Donor type: Deceased (brain death)	188 654	1.00	**0.74**	**0.71**	**0.74**	**<.001**	**<.001**	**<.001**
Donor type: Deceased (circulatory death)	16 481	1.00	0.70	1.18	**0.69**	.077	1.000	**<.001**
Donor cause of death (deceased donor): Trauma	86 576	1.00	**0.74**	**0.75**	**0.74**	**<.001**	**<.001**	**<.001**
Donor cause of death (deceased donor): Other	118 559	1.00	**0.74**	**0.68**	**0.74**	**<.001**	**<.001**	**<.001**

(Continues)

TABLE 2 (Continued)

Characteristic	Subcohort count (n)	Hazard ratio				*P*-value* vs United States		
		United States	Australia	New Zealand	United Kingdom	Australia	New Zealand	United Kingdom
Donor relationship to recipient (living donor): Sibling	36 653	1.00	**0.82**	0.87	**0.78**	**.044**	1.000	**<.001**
Donor relationship to recipient (living donor): Biologic nonsibling	44 694	1.00	**0.72**	0.81	**0.68**	**<.001**	.519	**<.001**
Donor relationship to recipient (living donor): Biologically unrelated	36 142	1.00	**0.79**	1.04	**0.73**	**.008**	1.000	**<.001**
Total ischemia time: Living donor <2 h	49 838	1.00	**0.78**	0.95	**0.68**	**<.001**	1.000	**<.001**
Total ischemia time: Living donor ≥2 h	67 651	1.00	**0.73**	0.81	**0.72**	**<.001**	.341	**<.001**
Total ischemia time: Deceased donor <20 h	115 945	1.00	**0.73**	**0.72**	**0.74**	**<.001**	**<.001**	**<.001**
Total ischemia time: Deceased donor ≥20 h	89 190	1.00	**0.78**	**0.68**	**0.75**	**<.001**	**<.001**	**<.001**
HLA mismatch: 0	29 611	1.00	**0.72**	0.88	**0.77**	**<.001**	1.000	**<.001**
HLA mismatch: 1	18 923	1.00	**0.76**	0.84	**0.80**	**<.001**	1.000	**<.001**
HLA mismatch: 2	44 988	1.00	**0.73**	**0.73**	**0.75**	**<.001**	**<.001**	**<.001**
HLA mismatch: 3	72 290	1.00	**0.70**	**0.69**	**0.71**	**<.001**	**<.001**	**<.001**
HLA mismatch: 4	63 922	1.00	**0.79**	**0.71**	**0.71**	**<.001**	**.002**	**<.001**
HLA mismatch: 5	62 448	1.00	**0.77**	0.92	**0.72**	**<.001**	1.000	**<.001**
HLA mismatch: 6	30 442	1.00	**0.73**	0.86	**0.69**	**<.001**	1.000	**<.001**
Year of transplant: 1988-1994	60 257	1.00	**0.83**	**0.75**	**0.78**	**<.001**	**<.001**	**<.001**
Year of transplant: 1995-1998	42 023	1.00	**0.73**	**0.78**	**0.74**	**<.001**	**.019**	**<.001**
Year of transplant: 1999-2002	49 174	1.00	**0.66**	**0.75**	**0.68**	**<.001**	**.013**	**<.001**
Year of transplant: 2003-2006	57 689	1.00	**0.71**	**0.66**	**0.65**	**<.001**	**.005**	**<.001**
Year of transplant: 2007-2010	62 971	1.00	**0.70**	0.85	**0.73**	**<.001**	1.000	**<.001**
Year of transplant: 2011-2014	50 510	1.00	**0.67**	1.05	0.90	**.033**	1.000	1.000

Bold face indicates statistically significant results. Each row below represents a separate Cox regression.
**P*-values were adjusted for multiple comparisons using stepdown Bonferroni method.

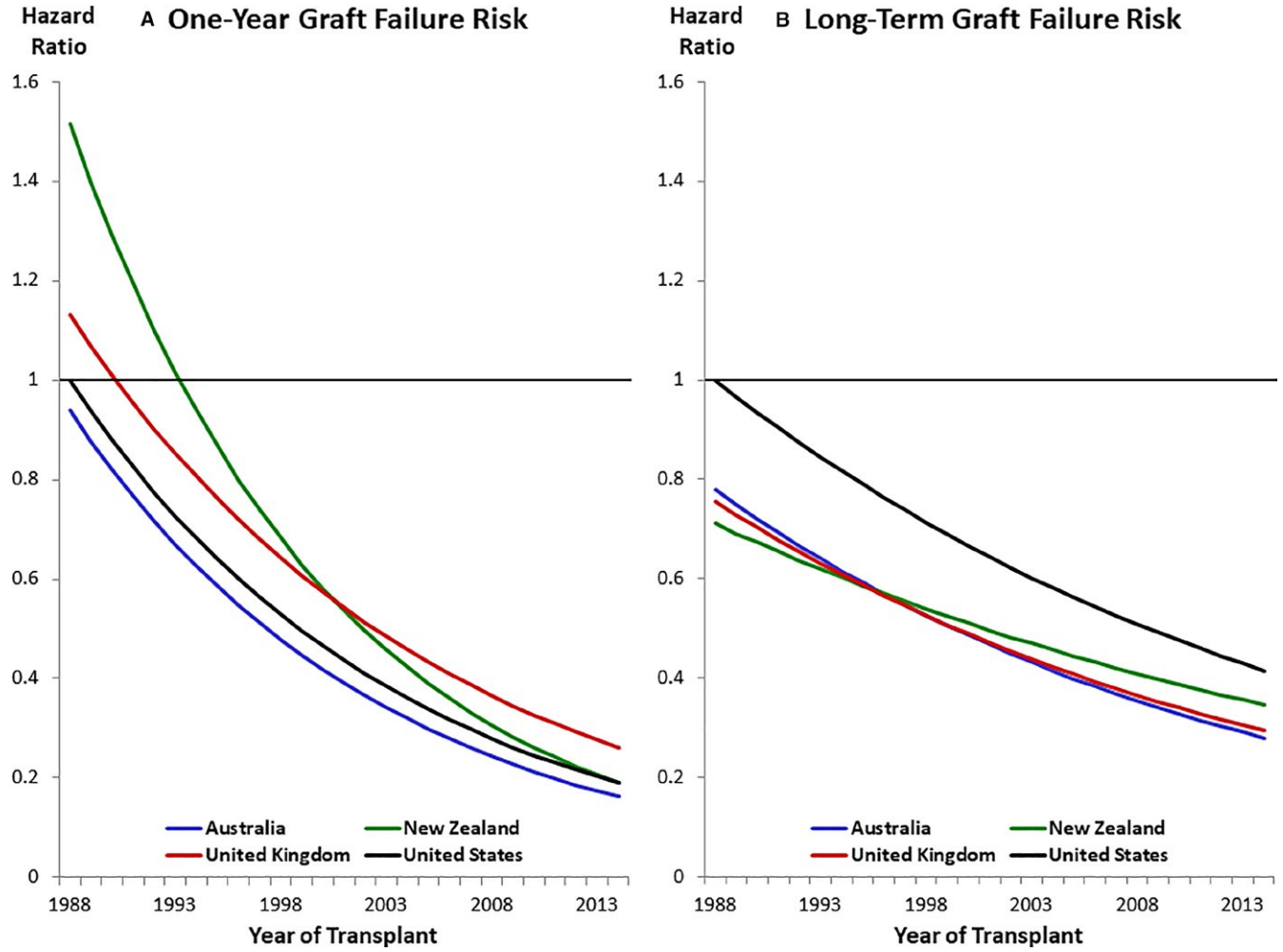

FIGURE 2 Trend in risk of graft failure over calendar time 1988-2014 by country (A) hazard ratio (HR) of graft failure within the first year and (B) long-term HR of graft failure conditional on being alive with a functioning graft at 1 year. The reference (HR = 1.0) is the risk of graft failure in 1988 in the United States

demonstrated in Australia, New Zealand, and the United Kingdom across almost all tested subcohorts of recipient and donor demographics, donor source, and transplant characteristics (eg, HLA mismatch). The result for the heterogeneous subcohort of recipient race other than white or Asian was an exception. Nonwhite, non-Asian recipients in Australia (principally Aboriginal) had significantly worse outcome than their nonwhite, non-Asian counterpart (overwhelmingly African American) in the United States. Although it is well established that Australian Aboriginal kidney transplant recipients have worse outcomes than nonindigenous 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 (eg, socioeconomics, pharmacogenomics, social systems, access to care) that may explain the disparate outcomes.

It was not surprising that both 1-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 4 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 4 countries.

The rates of improvement over time in long-term outcome in the United Kingdom and New Zealand did not differ significantly from that in the United States, whereas 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 datasets from all 4 countries; the 3 registries selected for this study had comparable data collection methods, analytical conventions, and longitudinal follow-up.

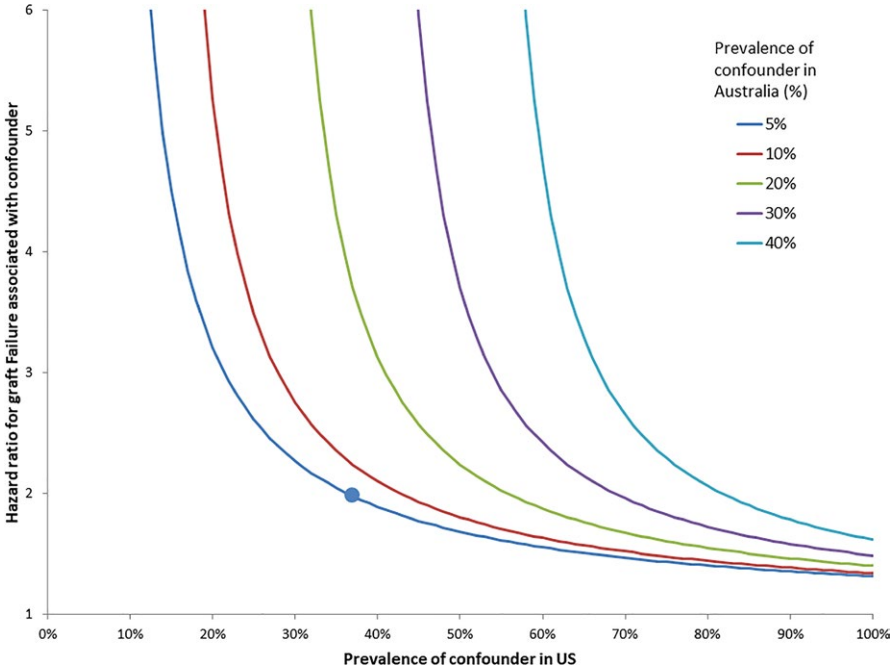

FIGURE 3 Effect of potential unmeasured confounder. The graph shows how large an effect and/or disparity in prevalence of a single confounder would need to be to explain the superior long-term graft outcome in Australia compared to the United States. For a given prevalence in Australia (each line represents 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 less in Australia would be necessary to negate the observed difference in long-term outcome. Adapted from Weintraub et al[12]

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 underascertainment 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 can reveal differences in outcomes that result from country-specific medical practice patterns or healthcare 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 3-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 healthcare insurance, there are other differences in health care systems and potentially identifiable differences in

posttransplantation 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 (eg, 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 posttransplantation care to test as best practices.

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DISCLOSURE

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

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SUPPORTING INFORMATION

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

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