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Time to Move on: HLA Matching Should Be Reconsidered in Modern Deceased Donor Kidney Allocation

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Background. HLA matching has been the cornerstone of deceased donor kidney allocation policies worldwide but can lead to racial inequity. Although HLA matching has been shown to improve clinical outcomes, the long-term impacts of non-allogenic factors are being increasingly recognized. This has led some transplant programs to include points for nonallogenic factors, for example, age. Our study looks at long-term graft and patient outcomes based on allocation cohorts rather than individual number of HLA mismatches. **Methods.** Using the Australia and New Zealand Dialysis and Transplant Registry, we analyzed 7440 adult deceased donor transplant events from 2000 to 2018. Transplants were classified as HLA matched or nonmatched according to the OrganMatch score and the local allocation algorithms. Graft function was studied with linear mixed modeling and graft rejection with logistic and binomial regression. Time to graft failure and recipient survival were examined with Kaplan–Meier curve and Cox regression models. **Results.** Forty percent of transplants were HLA matched. Mean glomerular filtration rate was 1.76 mL/min/1.73 m^2 higher in the matched transplants ($P < 0.001$). Matched transplants had longer time to graft failure (15.9 versus 12.7 y; $P < 0.001$) and improved recipient survival (risk of death hazard ratio, 0.83; $P = 0.003$). Matched recipients spent less time on dialysis (28.1 versus 44.8 mo; $P < 0.001$), and this significantly contributed to the benefits seen in graft loss and recipient survival. Caucasian recipients were more likely to receive a matched transplant than non-Caucasians. **Conclusions.** Matched transplants showed benefits in graft and recipient outcomes; however, some of these results were of small magnitude, whereas others seemed to be due in part to a reduction in time on dialysis. The benefit for the matched cohort came at the expense of the nonmatched cohort, who spent longer on dialysis and were more likely to be of a minority racial background.

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HLA matching has been a cornerstone of deceased donor kidney transplant policies worldwide for several decades.[1] In particular, matching at the HLA-A, -B, and -DR loci has been shown to increase graft survival compared with non-matched organs.[2-4] However, the advancement of immunological risk assessment and therapies now allows for successful transplantation in both well-matched and poorly matched deceased donor kidney recipients.[1] In addition, multiple non-immunologic factors have been demonstrated to significantly impact graft and recipient outcomes.[5-13] Some researchers have postulated that the role of HLA matching may therefore be losing clinical significance in the modern transplant era.[14] Concerns also exist around the disadvantage to racial minority groups in transplant systems that prioritize HLA matching over other factors.[15,16] Recipients of racial minority groups are less likely to find a favorable HLA match because of under-representation in the national donor pool and an increased tendency to HLA polymorphism.[17] Although deceased donor kidney allocation in Australia currently maintains a strong focus on HLA matching, other countries have adapted their transplant allocation policies to incorporate a broader range of influencing factors and improve equitable access to transplant.[18,19] Our study was designed to assess the clinical

outcomes and racial impact of the current deceased donor kidney allocation policy in Australia.

MATERIALS AND METHODS

We conducted a retrospective cohort analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Data are submitted prospectively to ANZDATA on an annual basis by nephrology units. Recipients aged 18 y and older who underwent deceased donor kidney transplantation between 2000 and 2018 were included. Recipients who received living kidney donor transplants, multiple organ transplants (eg, kidney and pancreas), and pediatric patients were not included. Approval for the study was obtained from ANZDATA and the Hunter New England Human Research Ethics Committee (authorization number: AU201903-17).

Cohorts

In the absence of a recorded allocation arm from ANZDATA, we used the OrganMatch score and the Transplantation Society of Australia and New Zealand allocation algorithms to divide recipients into HLA-matched and nonmatched cohorts. We reviewed current and previous iterations of the Transplantation Society of Australia and New Zealand national and state allocation algorithms to ensure that our historical groupings were accurate. The national allocation algorithm has been uniformly adopted by all the states in Australia to ensure that very well-matched kidneys (0-2 HLA mismatches) are distributed across state borders. If no such match was available, then the kidney was allocated in the state in which it was procured. Allocation algorithms varied between states but generally required a score equivalent to a maximum of 2 of 6 HLA mismatches, except for Victoria, which did not penalize for HLA-A mismatches and could have up to 3 of 6 mismatches in total. Kidneys that fulfilled these requirements were allocated as a State HLA allocation. Kidneys that could not be distributed on the basis of a favorable HLA match were allocated by scores determined largely by the number of months spent on dialysis by the recipient. For our study, both nationally allocated and State HLA allocations were considered as matched transplants. Allocations that were based largely on dialysis time without HLA matching were deemed nonmatched transplants. See Appendix 1 (SDC, http://links.lww.com/TXD/A405) for a complete explanation of the OrganMatch scores used to determine the matched and nonmatched cohorts for this study.

Transplants performed in Western Australia (N = 867) were unable to be included in the study as they were not divisible into clear cohorts. Western Australia allocated more points for each month on dialysis, which meant that a recipient with high mismatches but long dialysis time could receive a higher OrganMatch score than a recipient with fewer mismatches and shorter dialysis time. As such there was no clear numerical cutoff to divide into matched and nonmatched cohorts.

Statistical Analysis

Recipient demographics included were age, gender, race, smoking status, time on dialysis, primary renal disease, and comorbidities at the time of transplant (diabetes, lung disease, arterial disease, peripheral vascular disease, cerebrovascular disease). Donor demographics included were age and gender. Transplant-related variables were transplant state, total ischemic time, and induction immunotherapy. The primary outcome measures were graft function, graft rejection, graft loss, and recipient survival.

Comparison of recipient and donor demographics and transplant variables between matched and nonmatched transplants was performed using the Pearson chi-square test, independent t test, or Mann–Whitney U test. Graft function was measured over time (3 mo to 10 y posttransplant) as glomerular filtration rate (GFR) calculated using the Cockroft-Gault formula. GFR over time was compared between allocation groups using linear mixed modeling; fixed effects for group, months (categorical), an interaction term (group × months), and a random intercept for person (to account for within-person correlation) were included. Covariates including year of transplant, age, graft number, and comorbidities were added to modeling to account for potential confounding. An additional model was fit with a 3-way interaction term for allocation group, months posttransplant, and year of transplant (with main effects and all 2-way interactions).

Graft rejection was examined using both binary logistic regression (at least 1 rejection Y/N) and negative binomial regression (number of rejections; with offset for log length of time the graft was viable). Time to graft failure and overall patient survival were examined graphically using a Kaplan–Meier curve and compared between allocation groups using cox proportional hazard regression, with and without potential confounders. An additional model was performed for graft failure, controlling for competing risk of death using Fine and Gray methods. Graft failure because of nonimmunologic events such as vascular thrombosis, surgical complications, and cortical necrosis were excluded from this analysis. To examine whether the difference in time to graft failure or patient death changed over year of transplant, an additional model was fit with an interaction term for the allocation group and year of transplant. Mediation was performed for time to event outcomes to examine the percentage of the effect of the allocation group on time to event that was mediated through time on dialysis. Statistical analysis was performed using SAS V.9.4 (SAS Institute, Cary, NC) and was conducted by an independent statistics unit.

RESULTS

Data for 8814 transplants events were received from ANZDATA for the years 2000 to 2018. Exclusions were made for transplants performed in Western Australia (N = 867), missing OrganMatch scores (N = 460), and those with graft loss because of nonimmunological causes (N = 159; see Figure 1). Seven thousand four hundred forty deceased donor kidney transplant events in 7291 adult recipients were included in the analysis. Of the 7440 transplant events, 40% were matched transplants occurring at either the national or state level, and 60% were nonmatched transplants. See Table 1 for a breakdown of transplants allocated through either the national or state algorithms.

Demographics and Race

Recipient demographics are displayed in Table 2. The mean recipient age was 50 y for matched transplants and 51 y for nonmatched transplants. The mean donor age was 45 y for matched transplants and 47 y for nonmatched transplants.
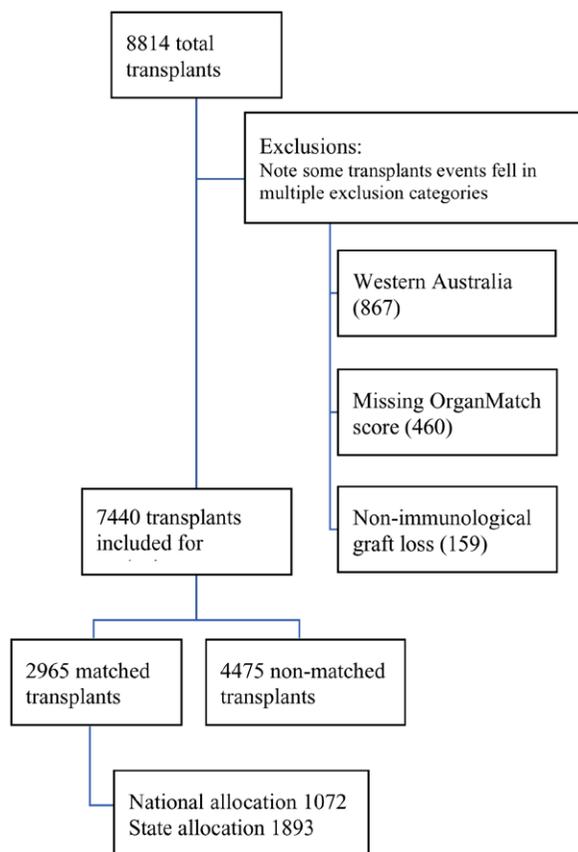
FIGURE 1. Inclusion and exclusion process.

The distribution of gender in both donor and recipient cohorts was similar. Coronary artery disease (15% versus 19%; $P < 0.001$) and diabetes (17% versus 23%; $P < 0.001$) were less prevalent in the matched group at time of transplant. Other comorbidities were similar between both groups. Matched transplants had a lower prevalence of diabetic nephropathy as the primary renal disease (11% versus 15%), and higher prevalence of polycystic kidney disease (15% versus 13%) and reflux nephropathy (9.5% versus 7.1%; $P < 0.001$). The total ischemic time and use of induction therapies were similar in both transplant groups (see Table 3).

Caucasian recipients were more likely to receive a matched kidney than recipients from minority racial backgrounds. Although Caucasian recipients constituted 76% of all transplants, they received 87% of matched kidneys. Conversely, Aboriginal and Torres Strait Islander, Pacific Islander, Maori, Asian, African, Middle Eastern, and European (other than Caucasian) recipients were all underrepresented in the matched group. There was a significant difference in the distribution of recipient race between the allocation groups ($P < 0.001$; see Table 2).

Matched recipients spent significantly less time on dialysis before transplant (median 28 versus 45 mo; $P < 0.001$). Caucasian recipients spent significantly less time on dialysis compared with non-Caucasian recipients (36 versus 43 mo; $P < 0.001$). Table 3 and Table 4 display the breakdown of dialysis time by allocation group and racial group.

Graft Function

Matched transplants seemed to have better overall early graft function compared with nonmatched transplants ($P < 0.001$; see results in Table 5). Small benefits in graft function were observed in the matched kidneys over time (GFR: 66 versus 64 at 1 y; $P < 0.001$; see Figure 2). On average, GFR was 1.76 mL/min/1.73 m² higher in the matched group (95% confidence interval [CI], 0.81-2.70; $P < 0.001$; main effect, averaged over time; see Figure 3 and Table 6). There was no difference in the trend in graft function over time between the matched and nonmatched transplants. The change in GFR over time was not impacted by the year of transplant in either group ($P = 0.978$).

Graft Rejection and Graft Failure

Graft rejection was analyzed as both a lifetime incidence and a rate of rejection episodes per year of kidney viability (see Table 5). Regression results for this analysis are displayed in Table 7. Matched transplants had a lower incidence of acute rejection episodes at any time posttransplantation (23% versus 30%; odds ratio, 0.71 [95% CI, 0.65-0.77]; $P < 0.001$). After accounting for potential confounding, the rate of acute rejection episodes per kidney year was significantly lower in the matched group (0.09 versus 0.13 rejections per kidney year; incident rate ratio, 0.70 [95% CI, 0.63-0.78]; $P < 0.001$). Of those who had rejection at any time, matched transplants were less likely to have an early rejection episode within 3 mo posttransplant (59% versus 68%; $P < 0.001$).

Results for graft failure are displayed in Table 5 with regression modeling displayed in Table 7. The median time to graft failure, accounting for censoring, was 15.9 y for matched transplants and 12.7 y for nonmatched transplants, $P < 0.001$. At the last follow-up, 88% of matched transplants and 86% of nonmatched transplants were functioning ($P = 0.007$). Matched transplants had a lower hazard of graft loss (hazard ratio [HR], 0.71 [95% CI, 0.62-0.81]; $P < 0.001$) as displayed in Figure 4. The hazard of graft loss did not change substantially after adjusting for competing risk of death (HR, 0.72 [95% CI, 0.63-0.83]; $P < 0.001$). After accounting for time on dialysis, the direct effect of allocation group showed slightly less graft survival benefit for the Matched group but was still significant, direct effect (HR, 0.76 [95% CI, 0.66-0.88]; $P < 0.001$). The causes of graft loss were similar between both groups: chronic graft loss because of interstitial fibrosis and tubular atrophy was most common (58%), followed by acute rejection (9.8%) and glomerulonephritis (7.4%).

Recipient Survival

Recipient survival analysis is displayed in Table 7. Median recipient survival, accounting for censoring, was >17.6 y in the matched group and 16.9 y in the nonmatched group. After accounting for confounders, the hazard of death was lower for matched transplant recipients (HR, 0.83 [0.73-0.94];

TABLE 1.

Division of allocation cohort at national and state levels

	Allocation group	Total (N = 7440)
Allocation group	Matched	2965 (40%)
	Nonmatched	4475 (60%)
Allocation level	National matching	1072 (14%)
	State matching	1893 (25%)
	State waiting	4475 (60%)

TABLE 2.

Demographics by transplant allocation group

Characteristic	Class/Statistic	Matched (n = 2965)	Nonmatched (n = 4475)	Total (n = 7440)	P
Recipient age (y)	Mean (SD)	50 (12)	51 (12)	51 (12)	<0.001
Recipient gender	Male	1864 (63%)	2858 (64%)	4722 (63%)	0.3809
	Female	1101 (37%)	1617 (36%)	2718 (37%)	
Donor age (y)	Mean (SD)	47 (17)	45 (17)	46 (17)	0.0010
Donor gender	Male	2565 (57%)	1634 (55%)	4199 (56%)	0.0599
	Female	1910 (43%)	1331 (45%)	3241 (44%)	
Racial background	Caucasian	2566 (87%)	3065 (69%)	5631 (76%)	<0.001
	Aboriginal/Torres Strait Islander	56 (1.9%)	253 (5.7%)	309 (4.2%)	
	Pacific Islander including Maori	36 (1.2%)	175 (3.9%)	211 (2.9%)	
	European	21 (0.7%)	42 (0.9%)	63 (0.9%)	
	Asian	198 (6.7%)	751 (17%)	949 (13%)	
	Africa/Middle East	39 (1.3%)	102 (2.3%)	141 (1.9%)	
	Not stated/other	30 (1.0%)	66 (1.5%)	96 (1.3%)	
Smoking status at commencement of dialysis	Never	1590 (54%)	2407 (54%)	3997 (54%)	0.9054
	Former	993 (34%)	1514 (34%)	2507 (34%)	
	Current	342 (12%)	503 (11%)	845 (11%)	
Chronic lung disease at transplant	No	2683 (93%)	4080 (94%)	6763 (93%)	0.3864
	Yes	198 (6.9%)	277 (6.4%)	475 (6.6%)	
Coronary artery disease at transplant	No	2417 (85%)	3455 (81%)	5872 (83%)	<0.001
	Yes	420 (15%)	790 (19%)	1210 (17%)	
Peripheral vascular disease at transplant	No	2652 (93%)	3932 (92%)	6584 (93%)	0.3313
	Yes	197 (6.9%)	320 (7.5%)	517 (7.3%)	
Cerebrovascular disease at transplant	No	2785 (95%)	4167 (95%)	6952 (95%)	0.1479
	Yes	135 (4.6%)	237 (5.4%)	372 (5.1%)	
Diabetes at transplant	No	2463 (83%)	3464 (77%)	5927 (80%)	<0.001
	Yes	495 (17%)	1008 (23%)	1503 (20%)	
Primary renal disease	Glomerulonephritis	1251 (42%)	1921 (43%)	3172 (43%)	<0.001
	Polycystic kidney disease	438 (15%)	582 (13%)	1020 (14%)	
	Diabetic nephropathy	315 (11%)	682 (15%)	997 (13%)	
	Reflux nephropathy	282 (9.5%)	316 (7.1%)	598 (8.0%)	
	Hypertensive nephropathy	193 (6.5%)	275 (6.1%)	468 (6.3%)	
	Other	353 (12%)	472 (11%)	825 (11%)	
	Uncertain/not reported	133 (4.5%)	227 (5.1%)	360 (4.8%)	

SD, standard deviation.

$P = 0.003$). However, after accounting for time on dialysis, the direct effect of allocation group on recipient survival was no longer significant (HR, 0.89 [0.78-1.01]; $P = 0.07$).

DISCUSSION

Matched transplants showed benefits in graft and recipient outcomes; however, some of these results were of small magnitude, whereas others seemed to be due in part to a reduction in time on dialysis. The small benefit in graft function over time for matched transplants would be regarded as clinically negligible by most transplant clinicians. The most notable benefit was a reduction in both early and overall graft rejection for matched transplants, which corresponded to a longer time to graft failure. However, adjusted modeling suggested that part of the benefit in graft survival time for the matched group may be because of a reduction in time on dialysis. Despite a longer time to graft failure for matched transplants,

TABLE 3.

Transplant details by allocation group

Characteristic	Class/statistic	Matched (N = 2965)	Nonmatched (N = 4475)	Total (N = 7440)	P
Transplant state	NSW	1298 (29%)	944 (32%)	2242 (30%)	<0.001
	VIC	1335 (30%)	1188 (40%)	2523 (34%)	
	QLD	1133 (25%)	543 (18%)	1676 (23%)	
	SA	709 (16%)	290 (9.8%)	999 (13%)	
Total ischemic time (h)	Median (Q1, Q3)	12 (9, 15)	12 (9, 15)	12 (9, 15)	0.0391
Prophylaxis (excluding basiliximab)	Yes	283 (9.5%)	413 (9.2%)	696 (9.4%)	0.6471
Prophylactic thymoglobulin	Yes	172 (6.9%)	227 (5.7%)	399 (6.2%)	0.0511
Time on dialysis (mo)	Median (Q1, Q3)	28 (16, 48)	45 (26, 73)	38 (21, 63)	<0.001

NSW, New South Wales; QLD, Queensland; SA, South Australia; SD, standard deviation; VIC, Victoria.

TABLE 4.

Months on dialysis by racial origin

	Racial origin	Median	IQR	P
Months on dialysis, dichotomous	Caucasian	36	20–61	<0.001
	Non-Caucasian	43	25–69	
Months on dialysis, all races	Caucasian	36	20–61	<0.001
	Aboriginal/Torres Strait Islander	45	27–73	
	Pacific Islander including Maori	47	31–75	
	European	21	14–35	
	Asian	47	27–70	
	Africa/Middle East	39	24–67	
	Not stated/other	28	14–40	

IQR, interquartile range.

the recipient survival benefit in that group was not as substantial, and lost statistical significance once dialysis time was accounted for.

Nonmatched transplant recipients had a significantly higher prevalence of metabolic diseases, such as coronary artery disease and diabetes, and a higher prevalence of diabetic nephropathy as the primary renal pathology. We considered

that these comorbidities may have contributed to the poorer outcomes in nonmatched transplants; however, this was not seen in adjusted modeling for graft function and recipient survival.

The benefits for matched recipients came at the expense of their nonmatched counterparts because of a significant difference in the time that both groups spent on dialysis before transplant. The points assigned in the allocation algorithms for number of HLA matches far outweighed other factors such as time waiting on dialysis. This meant that recipients with a low number of HLA mismatches could be offered a transplant soon after joining the waiting list, whereas recipients without a favorable HLA profile may wait for many years before receiving a kidney. This created significant inequity, with nonmatched recipients waiting for a median of 17 mo longer for a kidney than recipients of matched transplants.

In addition to the difference in time on dialysis, we found that certain racial groups were more likely to receive a well-matched kidney. Caucasian recipients were significantly overrepresented in the matched group, whereas recipients of all other racial backgrounds were more likely to receive a nonmatched transplant. Caucasian recipients spent significantly less time on dialysis compared with other racial groups, because of their overrepresentation in the matched cohort. As discussed previously, shorter time on dialysis seemed to convey independent benefits in time to graft

TABLE 5.

Graft and patient outcomes by transplant allocation group

Characteristic	Class/statistic	Matched (N = 2965)	Nonmatched (N = 4475)	Total (N = 7440)	P
Immediate graft function	Spontaneous fall in serum creatinine by 10% within 24 h	1432 (49%)	1842 (42%)	3274 (45%)	<0.001
	Spontaneous fall in serum creatinine by 10% between 48 and 72 h	202 (6.9%)	307 (7.0%)	509 (6.9%)	
	Poor immediate function. No spontaneous fall in serum creatinine	259 (8.8%)	360 (8.2%)	619 (8.4%)	
	No immediate function. No immediate fall >10% in serum creatinine	647 (22%)	1164 (26%)	1811 (25%)	
	Immediate function (fall in creatinine of at least 30% by day 7)	189 (6.5%)	296 (6.7%)	485 (6.6%)	
	Slow function (failure of creatinine to fall by at least 30%)	67 (2.3%)	107 (2.4%)	174 (2.4%)	
	Delayed graft function (requiring dialysis within 7 d of transplant)	132 (4.5%)	322 (7.3%)	454 (6.2%)	
GFR, mean (SD)	3 mo	63 (19)	62 (19)	63 (19)	<0.001
	6 mo	64 (19)	63 (20)	63 (19)	0.0018
	12 mo	66 (19)	64 (20)	65 (20)	<0.001
	5 y	65 (21)	63 (21)	64 (21)	<0.001
	10 y	65 (21)	61 (22)	63 (21)	0.0035
At least 1 rejection episode		670 (23%)	1356 (30%)	2026 (27%)	<0.001
No. of rejections	0	2295 (77%)	3119 (70%)	5414 (73%)	<0.001
	1	462 (16%)	1023 (23%)	1485 (20%)	
	2	133 (4.5%)	246 (5.5%)	379 (5.1%)	
	3	43 (1.5%)	59 (1.3%)	102 (1.4%)	
	4+	32 (1%)	28 (0.6%)	60 (0.8%)	
At least 1 early rejection (<3 mo) in transplants with rejection		393 (59%)	920 (68%)	1313 (65%)	<0.001
Graft status at last time point	Graft functioning	2624 (88%)	3864 (86%)	6488 (87%)	0.0065
	Graft lost	341 (12%)	611 (14%)	952 (13%)	
Cause of graft failure	Acute rejection	28 (8.5%)	62 (10%)	90 (9.8%)	0.2409
	Interstitial fibrosis and tubular atrophy	192 (58%)	339 (57%)	531 (58%)	
	Hyperacute rejection	2 (0.6%)	2 (0.3%)	4 (0.4%)	
	Vascular	4 (1.2%)	3 (0.5%)	7 (0.8%)	
	Glomerulonephritis	32 (9.7%)	36 (6.1%)	68 (7.4%)	
	Noncompliance	15 (4.6%)	30 (5.1%)	45 (4.9%)	
	Other	56 (17%)	122 (21%)	178 (19%)	

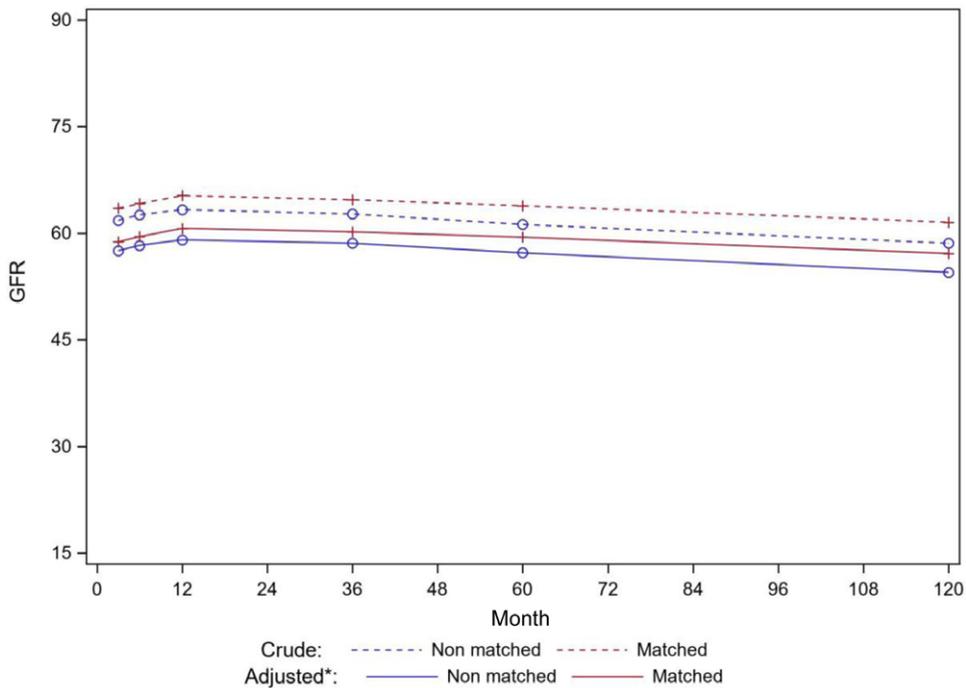GFR, glomerular filtration rate; SD, standard deviation.
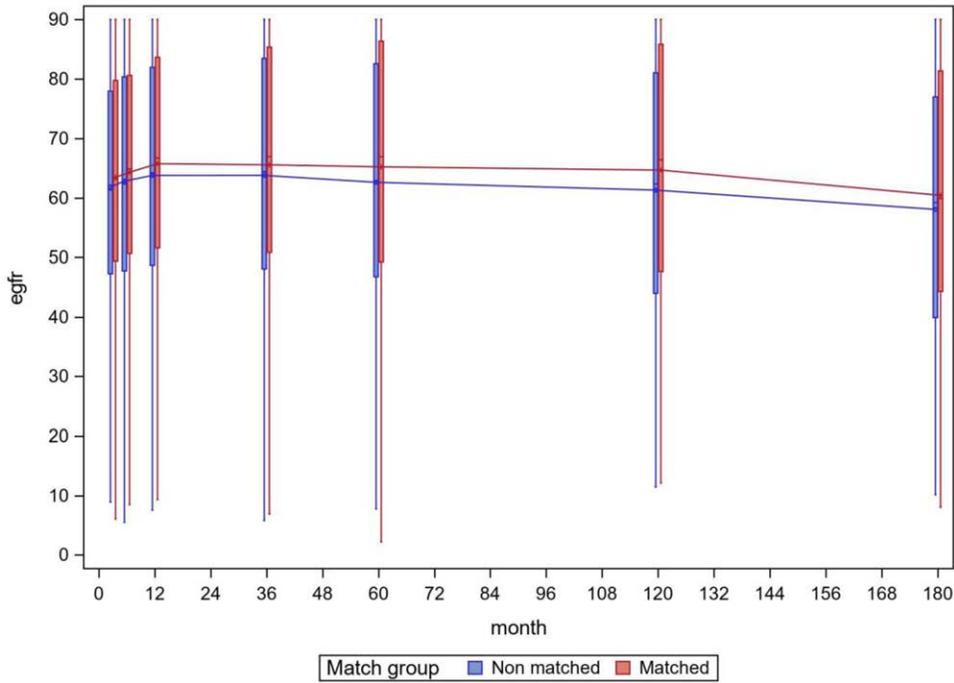
FIGURE 2. Graft function (GFR) over time by allocation group. eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

failure and overall recipient survival. These findings suggest that the allocation models in place at the time of this study, which prioritized HLA matching, resulted in significant racial inequity.

The global transplant community has become increasingly aware of racial disparities within deceased donor kidney transplantation. Indigenous and racial minority groups in Australia, New Zealand, Canada, and the United States have a disproportionately high burden of end-stage kidney disease but are less likely to receive a kidney transplant compared with Caucasians.[20-23] Racial minority groups are less likely to find a well-matched kidney in deceased donor transplant programs because of underrepresentation in the donor pool and genetic HLA polymorphism.[17]

*Adjusted for year (categorical), graft number, age, gender, race (Caucasian), and comorbidities.

FIGURE 3. Adjusted graft function (GFR) over time by allocation group. GFR, glomerular filtration rate.

TABLE 6.

Comparison of graft function (GFR) over time by allocation group

Model parameter	Crude Model, n	Crude P	Model, n	Adjusted[a] difference (95% CI)	P
Trends over time (interaction)	29 897	0.2528	26 918		0.3118
Group difference (averaged over time; main effect)	–	–	–	1.76 (0.81-2.70)	<0.001

[a]Adjusting for year (categorical), graft number, age, age squared, gender, Caucasian, lung disease, artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes.
CI, confidence interval; GFR, glomerular filtration rate.

Our results highlight equity issues that are particularly important in the Australian context. Aboriginal and Torres Strait Islander people in Australia have a lower life expectancy compared with nonIndigenous Australians, 8.6 y lower for males and 7.8 y lower for females.[24] Aboriginal and Torres Strait Islander people have a substantially higher incidence of end-stage kidney disease compared with nonindigenous Australians[25] and face multiple barriers in successfully receiving dialysis and kidney transplantation.[26-28] Aboriginal and Torres Strait Islander people are less likely to be placed on the waitlist for kidney transplant and spend longer on dialysis both before and after waitlisting.[15,20,22] Compared with a kidney transplant, prolonged time on dialysis causes increases in morbidity, mortality, and poor quality of life.[29-32] When Indigenous Australians do proceed to transplantation, our data demonstrate a longer dialysis wait time and a lower likelihood of receiving a well-matched kidney compared with Caucasian recipients.

Inequity in allocation models that prioritize HLA matching has historically been tolerated by the transplant community because the number of graft years gained from an excellent match—that is, the utility benefit—was considered to outweigh the equity issues that can arise. In the first few decades of deceased donor kidney transplantation, HLA matching had a crucial role in improving graft survival. Australian data from deceased donor kidney transplants in between 1971 and 1980 showed an overall 1-y graft survival of 54% and a 5-y survival of just 38%.[2] In the same study, mean 1-y graft survival was increased to 63% for matched transplants (0/4 HLA mismatch) compared with 50% for nonmatched transplants (≥3/4 HLA mismatches). At that time, the benefits of HLA matching were substantial and provided a significant overall utility benefit to the transplant program. However, as transplant science has evolved, the gap in outcomes between well-matched and poorly matched kidneys has narrowed.[33,34] Improvements in assessment and understanding of immunological factors now enable successful outcomes in both groups. Some studies show an improvement in long-term graft outcomes despite an increase in the average number of HLA mismatches over time[34] and a diminished significance of HLA matching.[14]

This does not mean that there is no longer a role for HLA matching. Despite the improved understanding of other immunologic and nonimmunologic transplant factors, HLA matching still seems to have a key role in kidney transplantation. HLA mismatches increase the risk of donor-specific antibody formation, resulting in graft rejection, graft loss, and sensitization against future transplantations. As our understanding of histocompatibility improves, matching at HLA-DR and HLA-DQ seems to be more important in reducing donor-specific antibody formation and its complications compared with matching at HLA-A and HLA-B.[35,36]

Many countries have adapted their allocation models to reflect evolving understanding of immunologic and nonimmunologic transplant factors and reduce inequities that arise from the HLA matching system. The United States Kidney Allocation System (released 2014) awards points for previous living kidney donation, 0 HLA mismatch, and years on dialysis.[37] It includes separate allocations to various subgroups, including allocation of the top 20% of kidneys (measured by

TABLE 7.

Regression modeling outcome analysis (ratios provided in relation to the matched cohort)

Characteristic	Class/statistic	Matched (N = 2965)	Nonmatched (N = 4475)	Result (95% CI)	Significance
Proportion of grafts with at least 1 rejection[a]	Estimated proportion (95% CI)	0.26 (0.23-0.28)	0.36 (0.33-0.40)	OR, 0.71 (0.65-0.77)	P < 0.001
Rate of graft rejection per viable graft year[a]	Average count/y (95% CI)	0.09 (0.08-0.11)	0.13 (0.12-0.15)	IRR, 0.70 (0.63-0.78)	P < 0.001
Time to graft failure (y)[b]	Median time to graft failure, crude (95% CI)	15.9 (14.2-17.7)	12.7 (12.3-13.8)	HR, 0.72 (0.63-0.83)	P < 0.001
Time to graft failure (y) mediated by months on dialysis[c]	Direct effect			HR, 0.76 (0.66-0.88)	P < 0.001
Recipient survival (y)[d]	Median time to survival, crude (95% CI)	NE	16.9 (16-NE)	HR, 0.83 (0.73-0.94)	P = 0.003
	Recipients at risk of death at 5 y, crude	1680 (56.7%)	2221 (49.6%)		
Recipient survival (y) mediated by months on dialysis[e]	Direct effect			HR, 0.89 (0.78-1.01)	P = 0.07

[a]Adjusting for year (categorical), graft number, and race (Caucasian).
[b]Adjusting for year (continuous), graft number, and race (Caucasian); accounting for competing risk of death.
[c]Adjusting for year (continuous), graft number, and race (Caucasian); accounting for competing risk of death; mediated by time on dialysis (mo). Percentage of indirect effect of allocation group mediated by time on dialysis: 47.6%.
[d]Adjusting for year (continuous), graft number, age, gender, Caucasian, lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes; survival did not reduce to 50% in the matched group; recipients at risk of death include those alive and uncensored.
[e]Adjusting for year (continuous), graft number, age, gender, Caucasian, lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes; survival did not reduce to 50% in the matched group. Percentage of indirect effect of allocation group mediated by time on dialysis: 57.4%.
CI, confidence interval; HR, hazard ratio; IRR, incident rate ratio; NE, not estimable; OR, odds ratio.

Product-Limit Survival Estimates
With Number of Subjects at Risk
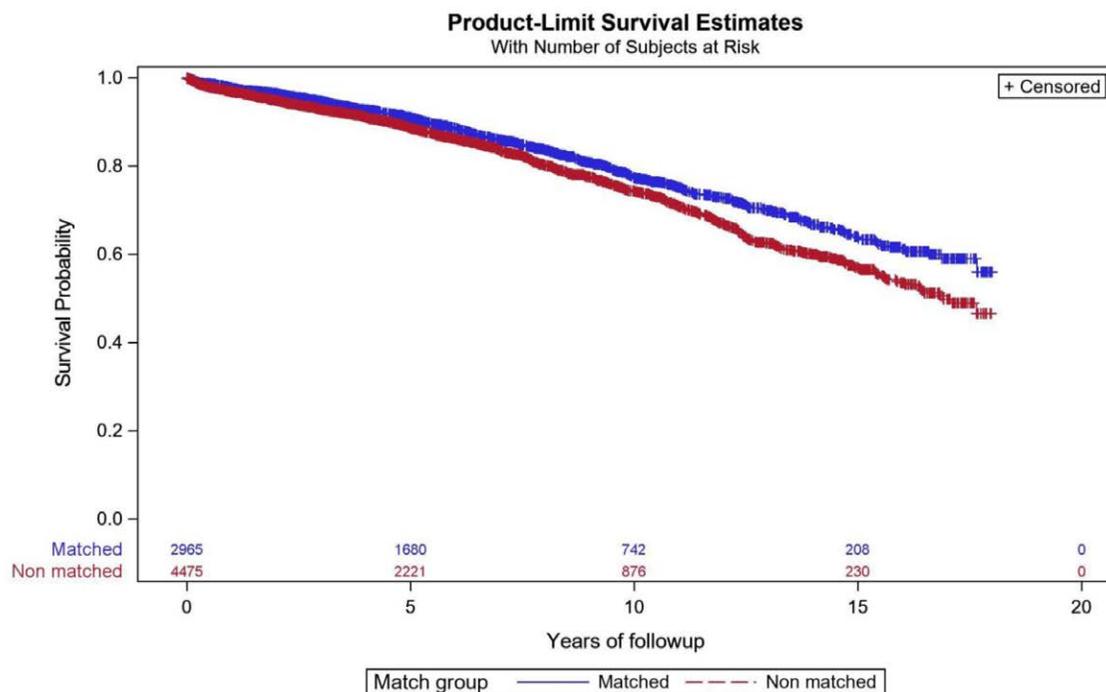
FIGURE 4. Time to graft failure by allocation group.

the Kidney Donor Profile Index, KDPI) to the 20% of recipients with the longest predicted survival (measured by the estimated posttransplant survival, EPTS). Matching at HLA-B (unless as part of zero mismatches) is no longer awarded a priority, a change that was made to improve equity for non-Caucasian recipients.[38] In this model, most kidneys are allocated with a strong emphasis on equity, whereas a smaller number will be allocated on the basis of maximum utility benefit. The United Kingdom has moved through several iterations of allocation models, most recently in 2019 with the Kidney Offering Scheme.[39] The current model attempts to improve both equity and utility. It aims to reduce waiting times for hard-to-match recipients (which includes racial minorities) and prioritizes those who have been waiting over 7 y. It has also introduced a longevity component that assesses donor and recipient risk indexes to maximize functional graft years.

Current deceased donor kidney allocation program of Australia was introduced in 1992 and attempts to balance utility (blood group and HLA typing) with equity (waitlist time). Since the completion of this registry analysis, updates have been made to the allocation program.[40] Recipient EPTS and KDPI calculations have been introduced to optimize graft–recipient survival matching and maximize utility. Allocations have been restructured to prioritize highly sensitized recipients. Finally, the states have adopted a single-uniform allocation policy that uses the EPTS-KDPI survival matching, followed by priority of 0-3 HLA mismatches and time on dialysis. Although these changes are encouraging, the current allocation model continues to focus strongly on HLA matching. Future iterations of the allocation model may consider elimination of matching at HLA-A and HLA-B altogether and prioritize recipients with uncommon antigens at HLA-DR and HLA-DQ.

The strength of our study lies in the scale and quality of data that are recorded by the ANZDATA database in Australia and New Zealand. ANZDATA provides the foundation for much

of Australia's kidney transplant research. Our study evaluated the outcomes of transplant recipients from multiple states, operating under varied allocation models and, therefore, provides a real-world analysis of Australia's HLA matching program. Our results are consistent with previous literature regarding both clinical outcomes and the racial disparities inherent in deceased donor transplant models that are built on HLA matching. Although we highlighted equity issues including longer time on dialysis for non-Caucasian recipients, we did not evaluate the clinical outcomes by racial group in this study. This is a necessary and urgent area of future research in Australian kidney transplantation. The mediation analysis that looked at the impact of dialysis time on outcomes was performed only on time to graft failure and recipient survival because of time and budget constraints. The difference in graft function between both groups was clinically insignificant, and as such additional analysis would be unlikely to add value. However, given there was a substantial difference seen in graft rejection between the matched and nonmatched groups, an assessment of the impact of dialysis time on this outcome may have added value to the discussion.

CONCLUSIONS

Our study has demonstrated that though there continue to be advantages for recipients of well-matched kidneys, the clinical benefit is of small magnitude and is due in part to a reduction in time spent on dialysis. Recipients of matched kidneys spent a significantly shorter average time on dialysis, and this conveyed a recipient survival benefit that was independent of matching status. Caucasian recipients were more likely to receive a matched kidney and therefore spent less time on dialysis than recipients of other racial groups.

Australia has recently made recent changes to the deceased donor kidney transplant allocation; however, work remains to ensure that the clinical benefit of HLA matching does not come

at the expense of racial minority groups. We hope that our findings will contribute to ongoing discussion and critical analysis of deceased donor kidney allocation. Transplant clinicians must carefully consider the future role of HLA matching and its negative implications for racial minority groups. Specific strategies to minimize the disadvantage to these groups, particularly for Aboriginal and Torres Strait Island people in Australia, must be incorporated in future allocation models.

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