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Kidney transplant results in children: progress made, but blacks lag behind

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Abstract

Early kidney transplant results in children lagged behind corresponding results in adults. Multiple advances over the last three decades have eliminated that gap. Most children now have equal or superior long-term allograft and patient survival compared to adult recipients. However, black children in the USA continue to have comparatively inferior allograft survival results to non-black children, even after extensive adjustments for socioeconomic status and access to transplantation.

Keywords

pediatric nephrology; chronic allograft nephropathy

Commentary

In the early days of kidney transplantation, patient and allograft survival in children lagged behind the results in adult recipients. Many reasons were attributed for this gap, including higher surgical technical difficulties, possible higher immune reactivity and variable drug metabolism in children. Thankfully, progress was made in many of these issues over the last 3 decades^{1, 2}. Technical difficulties were overcome, the faster drug metabolism of young children was adjusted for, and immune reactivity was studied. Multiple prospective trial consortia were developed and were able to overcome the challenge of obtaining meaningful conclusions in pediatric studies, often hurt by inadequate sample sizes in single center studies.

In this issue of the journal, Laskin and colleagues use large national registry data to depict one of the net results of all these advances: a substantial improvement in patient survival in pediatric recipients over the last 25 years. Each one-year increment in calendar year of first

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transplant was associated with a 2-3% lower adjusted risk of patient death, including deaths with a functioning graft. This group had previously documented the substantial improvements in patient survival in children on dialysis over the same time period³. At least in countries where patients have abundant access to advanced treatments for end-stage kidney disease, pediatric nephrologists can proudly counsel parents about excellent long-term outcomes for both dialysis and transplantation in the treatment of end-stage renal disease in children.

Unfortunately, these improvements have not been uniform across all populations in the USA, where the vast majority of patients with end-stage kidney disease have access to a dialysis or transplant center. Twenty to twenty-five years ago, black children in the USA had worse allograft results than non-black children. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which includes a registry of transplant recipients since 1988⁴, show a 10 percentage-point improvement in recent years in 7-year allograft survival across both non-black and black recipients (Figure). Most of the improvement has occurred in the first post-transplant year. Black children also experienced a 10-point improvement in 7-year allograft survival, but were roughly 20 percentage points behind non-black children in the older era and remain nearly that far behind in the recent era. Data from the 2012 annual report of Scientific Registry of Transplant Recipients in the USA (available at <http://srtr.transplant.hrsa.gov/ADR.aspx>) show a similar gap of 10 percentage points in 5-year allograft survival between black versus white adult kidney transplant recipients.

Part of this discrepancy was attributed to the much lower rate of living donor kidney transplantation in black children (34% versus 56% in non-blacks), which is associated with poorer long-term allograft survival in the general transplant population. Yet NAPRTCS data have also shown that the gap between living donor and deceased donor results has narrowed over the years⁴. In another article in this issue of the journal, Patzer et al remind us that black children have also historically suffered from higher rates of poverty, lack of access to advanced medical care and even reduced access to transplantation than their non-black counterparts. For a long time, worse allograft survival in children versus adults was attributed to these socioeconomic factors, with the underlying premise being that if we could control for or improve these socioeconomic barriers, then the results would be equal. Such a premise has been questioned, since most states within the USA have laws and programs that protect minors and therefore provide access to medications and transport to medical appointments.

Patzer and colleagues explore this hypothesis in great detail in this issue by using large national registry data to control for these socioeconomic issues. They show that results in black, but not Hispanic, children remain inferior even after controlling for multiple donor, transplant, immunological, immunosuppression and insurance covariates, pointing to possible additional unknown biological causes for the discrepancies. Many of these potential biological causes seem to specifically affect *long-term* allograft survival. NAPRTCS data also highlight that allograft survival is roughly equal between black and non-black children in the first year post-transplant in the most recent era (Figure). It is after the first year that

black children experience a significant drop in cumulative allograft survival, with a slope that is steeper than in non-black recipients.

Biologists have speculated about possible biological differences in transplantation outcomes across races for many years. Historically, Patzer et al highlight that pediatric black recipients have twice the rate of graft failure, reduced rates of waitlisting and preemptive transplantation, and poorer HLA matches than white recipients. Detailed HLA typing used in transplant immunological matching was originally delineated from studies that had lower frequencies of minority populations. Plus, African ancestry populations have greater number of HLA polymorphisms than other populations⁵. HLA matching of donor kidneys to black recipients may therefore be suboptimal, even when we think we have accounted for major antigen matching that is adequate for many non-black recipients. For example, one could speculate that more extensive HLA polymorphisms in black recipients could lead to subclinical humoral immune responses to minor HLA antigens (e.g., non-donor-specific HLA antibodies) that produce chronic allograft injury and reduce long-term graft survival. Tacrolimus metabolism is based on cytochrome p450 enzyme subtypes, which are substantially different in black versus non-black populations⁶. We now have biological evidence to partially explain why black populations have more severe chronic kidney disease, through the discovery of the APOL1 gene allele polymorphisms that confer higher risk for progression to end-stage kidney disease due to lesions within the focal and segmental glomerulosclerosis spectrum, regardless of socioeconomic factors⁷. Recent retrospective studies indicate that in kidney transplantation, the APOL1 status of the donor may have greater impact on graft survival than the APOL1 genotype of the recipient. In fact, Lee et al demonstrated that allografts from African-American donors without two APOL1 risk alleles had similar survival to those from European-American donors, thereby abrogating the traditionally poorer allograft survival attributed to African-American donors. Moreover, 75% of grafts lost with two APOL1 risk alleles had glomerulosclerosis versus only 12% of grafts lost with 0/1 risk alleles⁸. The presence of biopsy-proven lesions on the focal and segmental glomerulosclerosis spectrum is an important risk factor for subsequent graft loss in adults and children. One could speculate that the racial disparities in long-term allograft survival are due to a higher risk for recurrent FSGS due to APOL1 risk variants that are more likely to exist in black donor-recipient pairs. Interestingly, the subgroup analyses performed by Patzer et al showed that excluding subjects with focal and segmental glomerulosclerosis had no effect on racial disparities in graft survival in deceased donor recipients, but actually enhanced the effect of racial disparities in living donor recipients, suggesting that the impact of race on allograft survival was not exclusively due to a higher risk for recurrent focal and segmental glomerulosclerosis or the APOL1 genotype of the recipient, since APOL1 risk variants are limited to patients of African descent. Therefore, the true impact of APOL1 donor-recipient genotypes on racial disparities in allograft survival needs to be explored further.

Likely, many more such biological mediators exist and need to be discovered. The differential biology in black children should be a focus area of future studies in kidney transplantation. Children are unique in that they have a much lower death rate than older adults, allowing for higher quality studies of those factors which impact long-term allograft survival, separate from patient survival.

Both the Laskin et al and Patzer et al studies make use of large registry data. In the United States, such transplant or renal failure registries were founded in the late 1980s under federal government mandates. The availability of such large and continuously active registries has allowed for large-scale longitudinal analyses across an entire country's kidney transplant population at relatively low cost. The use of real world patients from national registry data allows for greater generalizability of the results to larger populations. These registries are administratively collected retrospective data with a fair proportion of missing data, so their limitations are not trivial. Yet the limitations of prospective trials are also not trivial. Prospective trials are very expensive to conduct and utilize highly selected populations, typically with short-term outcomes to control costs. To address biological differences that make transplantation results in black children inferior, we will need prospective trials to discover and validate the mechanisms underlying these differences, along with high-quality registry data to confirm an improvement in long-term outcomes.

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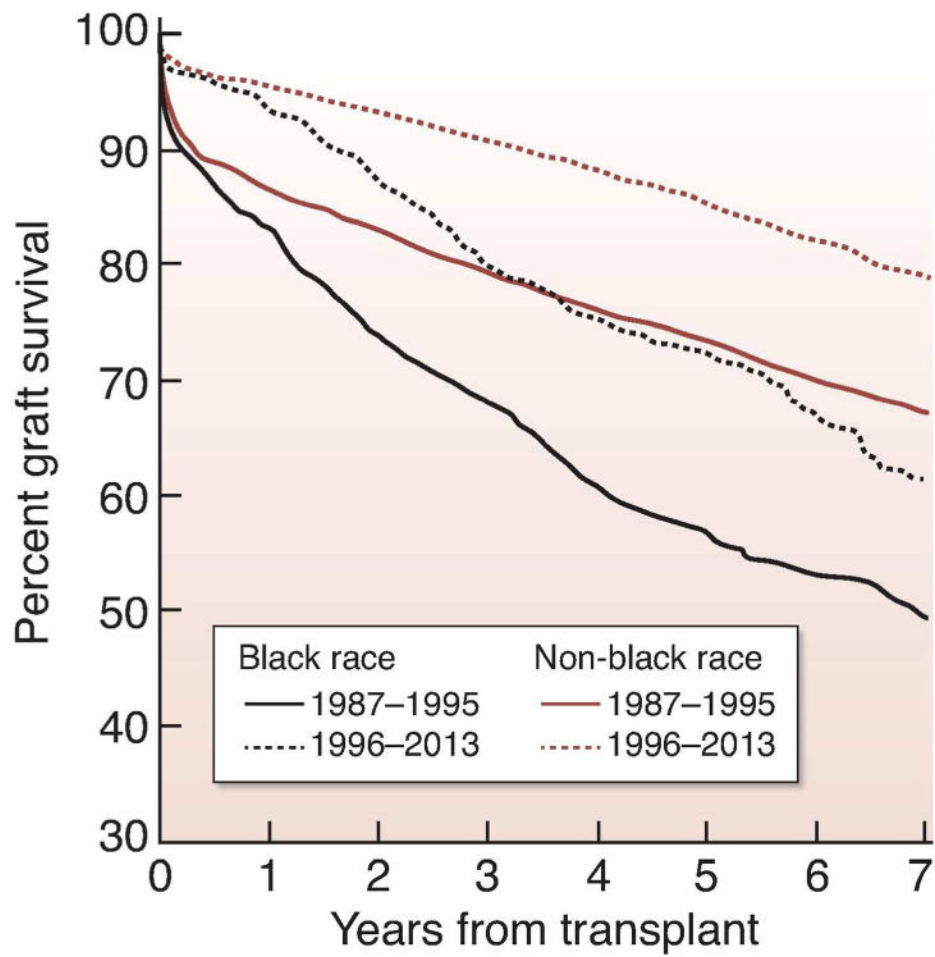


Figure. Kidney allograft survival in children in prior eras (solid lines) and more recent eras (dotted lines), separated by recipient non-black race (red color) or black race (black color). Graph prepared by Karen Martz from Emmes Corporation using data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), used with permission.