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The Risk of Failure With HLA Mismatch and Recipient Age in First Pediatric (<18 years) Kidney Transplants

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Background. Even in the modern era of kidney transplantation with improved surgical techniques, immunosuppression, and clinical care, HLA matching has been shown to be important in allograft survival in adults who receive an organ from either a deceased or living donor. We now explore the impact of genetic matching in pediatric first-kidney transplants. **Methods.** Using the United Network for Organ Sharing data, we identified 18 602 first pediatric (<18 years) kidney transplants between October 1, 1987, and December 31, 2016. Recipients were classified by number of HLA mismatches and donor origin. Cox proportional hazard analyses, adjusting for recipient and donor transplant covariates, were performed to study the impact of HLA on kidney allograft survival. **Results.** For the fully adjusted Cox model there was a 30% increase in the hazard of allograft failure for 1 HLA mismatch, when compared with 0 mismatched recipients, and a 92% increase in risk for 6 mismatches. Although pediatric allografts from living donors survive as long or longer than those from deceased persons, they have a higher hazard of failure as a function of HLA mismatch. Kidney allografts from deceased donors HLA mismatched 0 to 3 were found to survive as long as organs from living donors HLA mismatched 4 to 6. In the full Cox model, there was a strong, linear effect on the hazard of allograft failure with quartile of age such that the youngest patients at age of transplant had the longest surviving grafts. **Conclusions.** HLA plays an important role in the survival of first pediatric kidney transplants. The better the match, and the earlier the transplant is performed in the child's life, the lower is the risk that the organ will fail.

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The history of pediatric kidney transplantation has combined increased surgical expertise with improved clinical treatment that incorporates modern immunosuppression regimens, resulting in prolonging the survival of transplanted organs and recipients.[1] We have recently used the United States Kidney Transplantation data to look at the importance of HLA matching in the survival of allografts in adults (≥18 years) from deceased and living donors.[2,3] In the presence of modern drug therapies, we found that matching for the histocompatibility loci is still an important component in organ survival in adults. We now turn our attention to first kidney allografts in recipients younger than 18 years and investigate the role of genetic matching and growth and development in this population, in which HLA mismatch and age have been reported as risk factors for allograft failure.[4-10]

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MATERIALS AND METHODS

The pediatric data were taken from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) database and included all first kidney-only transplants in children (age, < 18 years) stratified by UNOS region from October 1, 1987, to December 31, 2016.[11] Allograft survival was censored at the last recorded examination, at the start of renal replacement therapy, or at death.

Variable Definitions

Table 1 lists the variables that were included in the analyses. Imputation by regression was employed to assign values to categorical variables with unknown or missing values. Donor and recipient ages were defined in year-quartiles. Variables recipient sex, donor sex, recipient ethnicity, peak-reactive antibody, donor source, immunosuppression therapies at discharge, HLA mismatch, and a variable that represents the 27 permutations of HLA-A, -B, and -DRB1 mismatch were defined as previously described.[2,3] Induction with antibodies was defined as a bivariate, yes or no, variable. Transplant era has 5 categorical values: 1987 to 1992, 1993 to 1997, 1998 to 2002, 2003 to 2007, 2008 to 2012, and 2013 to 2016. The underlying disease variable has 14 values that reflect the 12 most common diseases in the UNOS database and approximately 66% of the total disease states (Table 1).

Statistical Methods

SAS Institute software version 9.4 was used for all analyses.[12] HLA mismatches (0-mismatch reference) were the primary explanatory variable. Multivariate Cox proportional hazard regression analyses for the reduced and full models were performed by standard methods.[13,14] Tests for the proportional hazard assumption were performed by ordinary least squared regression of the Schoenfeld residuals on kidney survival time.[13] Cumulative sums of the martingale-based residuals tested the goodness of fit of the full proportional hazards model.[2,3,15,16] For all pediatric donors, the 18 602 records were sorted by risk score and divided into 31 groups while using the 31st group as reference. The expected number of events using the martingale residuals were used to calculate the z score for each group and to test the fit of the z score distribution to a $N(0,1)$ normal distribution.

We tested the equality of the hazard ratios (HRs) of the within mismatch category permutations by creating index variables (0,1) for each triple, including all variables in the full model of the Cox regression with at least 1 mismatch, and then comparing all permutations within a category.[13] The sequential Holm-Bonferroni procedure adjusted the P values.[17]

Linear models were fitted to the mismatches and the HRs using the algorithm as previously described.[2,3]

RESULTS

Pediatric Recipient Cohort

The data included a total of 18 602 first-kidney-alone transplant records in children less than 18 years of age with data that were obtained between October 1, 1987, and December 31, 2016. There was a total of 124 316 years of kidney allograft follow-up time. Mean follow-up was 6.7 years with a Quartile 1 (Q1) of 2.2 years, median of 5.3 years, and Q3 of 9.9 years. The longest surviving kidney allograft was 29.1 years. Females represented 7681 recipients with a mean age of 11.3 years; male recipients numbered 10 921 with mean age 10.5 years. A total of 8030 children received an organ from a related donor, 9714 recipients an allograft from a deceased donor, and 858 recipients received an organ from an unrelated living donor.

The distribution of covariates incorporated into the Cox proportional hazard regressions, stratified by HLA mismatch, is found in Table 1. Females represented 8396 of the donors with a mean age of 31.3 years, whereas there were 10 206 males in the donor pool with a mean age 27.8 years.

Kaplan-Meier (KM) projected median survival for all pediatric kidneys was 14.8 years with 95% confidence interval (95% CI, 14.4-15.5). In **Figure S1 (SDC,** http://links.lww.com/TXD/A107), the KM curves are presented for the living donor organs, stratified by relation. The Log-Rank statistic for the differences of the survival curves, comparing related versus unrelated, did not reach statistical significance, 2.86 (1 df, $P = 0.0906$). Therefore, the 2 living strata were grouped for further analyses.

Test of the Goodness-of-fit for the Full Cox Multivariate Proportional Hazards Models

For the pediatric cohort in the full Cox model, the proportional hazard assumption was valid for each of the 10 explanatory variables in an ordinary least squared regression of the Schoenfeld residuals on kidney survival time (**Table S1, SDC,** http://links.lww.com/TXD/A112). The test of the goodness of fit of the proportional hazards model produced the expected normal Z distribution with a mean of 0.0 and standard deviation of 1.0 (**Table S2, SDC,** http://links.lww.com/TXD/A113; **Figure S2, SDC,** http://links.lww.com/TXD/A108).

Impact of Number of HLA Mismatches on Pediatric Kidney Allograft Survival

A KM, unadjusted analysis was performed for all the pediatric allografts in the UNOS database, 1987 to 2016, stratified by HLA mismatch (Figure 1). The curves generally cluster in 2 groups, mismatch categories 0 to 2 and 4 to 6, with 3 mismatches being intermediate. To study the role of HLA mismatch in more detail and its effect on the survival of pediatric allografts, the data were incorporated into Cox multivariate regressions to estimate the hazard of failure by HLA mismatch when adjusted by a vector of covariates. Table 2 presents the HRs from full model Cox regressions for the pediatric allografts, overall, and stratified by donor source, living and deceased. For all 18 602 pediatric recipients, compared with children with 0 mismatch, there was a 30% higher risk of allograft failure for 1 mismatch and a 92% higher risk for 6 mismatches (reduced Cox multivariate regression models and covariates removed from final regressions are found in **Tables S3 and S4, SDC,** http://links.lww.com/TXD/A114, http://links.lww.com/TXD/A115).

Allografts from living donors exhibited higher risks of failure attributable to HLA mismatch: 48% for 1 mismatch and 2.14 times more than the reference, 0 mismatch, for 6 mismatches. Deceased donor organs, which had the lowest vector of HRs, showed a 16% higher risk for 1 mismatch and 62% higher risk of failure for 6 mismatches (Table 2). As with the KM curves, the HR differences sorted into 2 clusters, 1 to 3 and 4 to 6 mismatches (Figure 2). For 4 and 5 mismatches,

TABLE 1.

Baseline data for 18 602 pediatric first kidney transplants by HLA mismatch, 1987-2016[a]

Variables	Number	HLA mismatch (%)							*df*	*P*
		0	1	2	3	4	5	6		
Recipient age, y									18	<–0.0001
Quartile 1, 0-7	5244	2.9	5.8	19.2	29.1	16.5	17.5	9.0		
Quartile 2, >7-12	4377	2.9	5.8	17.6	27.4	17.2	19.5	9.6		
Quartile 3, >12-15	4644	3.6	5.2	16.2	26.4	17.6	20.9	10.1		
Quartile 4, >15 to <18	4337	4.1	4.8	13.8	24.2	18.8	22.3	12.0		
Donor age, y									18	<0.0001
Quartile 1, 0-20	4962	3.0	1.5	4.6	14.0	27.0	33.4	16.5		
Quartile 2, >20-30	4736	4.1	4.1	12.3	22.0	20.6	23.3	13.6		
Quartile 3, >30-39	4649	3.2	8.2	25.5	37.1	10.4	11.0	4.6		
Quartile 4, >39	4255	3.2	8.4	26.7	36.1	10.6	10.2	4.8		
Transplant era									30	<0.0001
1987-1992	2709	4.8	7.8	23.0	32.4	15.6	12.3	4.1		
1993-1997	2968	4.2	7.6	22.4	31.7	15.5	12.9	5.7		
1998-2002	3105	4.1	6.4	20.3	30.7	15.5	15.5	7.5		
2003-2007	3689	3.0	5.1	14.0	25.1	18.3	23.0	11.5		
2008-2012	3526	2.1	3.3	12.3	21.0	19.6	26.2	15.5		
2013-2016	2605	2.2	2.6	10.0	21.6	20.0	28.3	15.3		
Recipient sex									6	NS
Female	7681	3.4	5.4	16.4	26.1	17.4	20.6	10.7		
Male	10 921	3.3	5.5	17.1	27.4	17.5	19.5	9.7		
Donor sex									6	<0.0001
Female	8396	3.5	6.3	19.8	30.7	14.9	16.4	8.5		
Male	10 206	3.3	4.7	14.4	23.8	19.6	22.8	11.4		
Recipient ethnicity									30	<0.0001
Hispanics	3964	3.1	4.5	13.7	23.7	20.1	22.8	12.1		
Asians	565	2.3	4.4	13.8	15.6	23.2	27.1	13.6		
Non-Hispanic blacks	3433	0.9	2.1	10.2	20.8	20.7	28.3	17.0		
American Indians	168	2.4	7.1	13.7	16.1	23.2	30.4	7.1		
Pacific Islanders	70	1.4	2.9	5.7	27.1	20.0	24.3	18.6		
Non-Hispanic whites	10 402	4.3	6.9	20.5	30.9	15.0	15.5	6.9		
Donor source									12	<0.0001
Deceased	9714	2.3	1.3	4.1	13.0	28.6	33.7	17.0		
Living-related	8030	4.9	10.8	33.0	44.5	3.2	2.4	1.2		
Living-unrelated	858	0.7	2.2	10.3	19.5	24.8	27.1	15.4		
Underlying disease									78	<0.0001
Congenital dysplasia	2477	3.4	5.1	16.7	27.0	17.4	20.5	9.9		
Focal glomerular sclerosis	2061	2.4	4.9	12.1	22.4	20.8	25.4	12.0		
Congenital obstructive uropathy	1835	3.2	5.7	17.7	28.4	17.7	19.6	7.7		
Chronic glomerulonephritis unspecified	1070	4.2	6.2	19.0	30.3	15.9	16.0	8.4		
Chronic pyelonephritis/reflux nephropathy	759	4.5	7.0	17.8	27.2	15.4	18.6	9.5		
Polycystic kidneys	682	2.9	4.4	17.9	29.5	16.9	18.6	9.8		
Acquired obstructive nephropathy	595	4.9	7.9	19.7	31.4	17.6	12.6	5.9		
Hemolytic uremic syndrome	457	2.2	5.9	19.9	25.6	17.3	21.4	7.7		
Alport syndrome	453	3.3	4.0	13.7	18.7	22.1	22.3	15.9		
Prune belly syndrome	411	3.7	5.1	17.5	33.3	14.8	13.4	12.2		
IGA nephropathy	328	2.4	3.7	18.3	27.1	15.9	20.1	12.5		
Systemic lupus erythematosus	317	3.2	2.2	14.5	24.0	18.9	23.0	14.2		
Other diseases/states	6722	3.3	5.5	17.4	26.8	16.8	19.8	10.4		
Not reported	435	5.8	5.5	14.9	28.5	17.9	17.7	9.7		
Induction therapy at transplant									6	<0.0001
Yes	14 117	3.0	5.1	15.7	26.0	18.1	21.1	11.0		
No	4485	4.4	6.4	20.4	29.6	15.7	16.2	7.3		

Continued next page

TABLE 1. (Continued)

Variables	Number	HLA mismatch (%) 0	1	2	3	4	5	6	*df*	*P*
Maintenance therapy at discharge									48	<0.0001
Maint236: tacrolimus, mycophenolate, ± steroids	7687	2.4	4.1	13.3	23.7	18.6	24.7	13.2		
Maint146: cyclosporin, azathioprine, ± steroids	3816	4.2	8.1	23.9	32.5	15.2	11.7	4.4		
Maint136: cyclosporin, mycophenolate, ± steroids	1799	4.1	7.1	19.4	31.9	16.4	14.3	6.8		
Maint36: mycophenolate, ± steroids	642	3.1	4.7	12.4	22.3	19.5	25.2	12.8		
Maint16: cyclosporin, ± steroids	775	5.3	7.0	17.3	28.1	15.6	18.6	8.1		
Maint26: tacrolimus, ± steroids	794	3.4	3.8	16.2	25.2	18.4	19.4	13.6		
Maint156: cyclosporin, rapamycin, ± steroids	95	5.2	4.2	27.4	27.4	10.5	17.9	7.4		
Maint46: azathioprine, ± steroids	399	7.8	10.8	19.5	27.8	18.3	12.3	3.5		
Other maintenance therapy	2595	3.3	3.8	15.5	25.5	18.2	22.1	11.6		
HLA mismatch	18 602	3.4	5.4	16.8	26.9	17.5	19.9	10.1		

the 95% CIs exclude one another. Differences in the HRs occurred despite the large variation in the distribution of the HLA mismatches in these categories, in which many more recipients of deceased organs were mismatched for 4 to 6 HLA alleles (Figure 3).

To test the importance of grouped HLA mismatches when stratified by donor source, we ran a fully adjusted Cox model with a new categorical variable with 4 values, deceased 0 to 3, deceased 4 to 6, living 0 to 3, and living 4 to 6 mismatches, with deceased 0 to 3 as the reference (Table 3). The HR for living donor allografts with 4 to 6 mismatches was not statistically different from the reference. If one calculates unadjusted K-M curves, the 50% or median survival CIs overlap: for deceased donors 0 to 3, the median survival is 11.9 years (95% CI, 11.0-12.8 years), whereas for living 4 to 6, it is 13.3 years (95% CI, 11.7-16.4 years).

HLA-A, -B, and -DRB1 mismatches were further analyzed in 27 [A, B, DRB1] triples and incorporated into a full Cox regression (Table 4). Only 5 of the permutations had an HR that was not a statistically significant risk factor for earlier kidney failure when compared to the reference [0, 0, 0]. The remaining 22 permutations had a statistically significant higher risk of allograft failure ranging from 37% for triple [0, 1, 0] ($P = 0.0105$) to 2.55 times the reference for permutation [2, 0, 2] ($P < 0.0001$).

When the mismatch triples were incorporated into tests of differences within each mismatch category, none of the 57 tests was found to be statistically significant when corrected for multiple tests (**Table S5, SDC,** http://links.lww.com/TXD/A116). Comparison [0, 2, 1]:[1, 1, 1] in mismatch category 3 had the lowest observed *P* value of 0.0033, but did not reach the adjusted value of 0.0009.

Covariate results for the overall, full Cox regression are found in Table 5. Older recipient age is highly associated as a risk factor for decreased allograft survival for each quartile, when compared with Q1, and increased with age. Female recipients were at a higher risk for graft failure, whereas organs from female donors were also at higher risk. When compared with the earliest era category in the data (1987-1992), there is a progressive, highly significant increase in the survival of pediatric kidneys from 1993 to 2016.

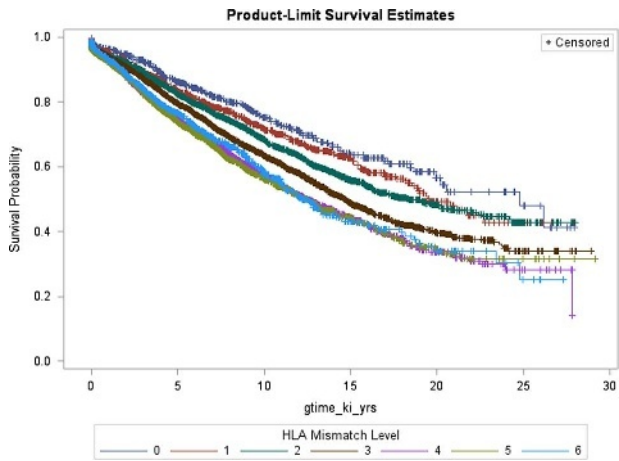

FIGURE 1. KM curves were fitted to the unadjusted survival data for 18 602 pediatric (<18 years) first kidney transplants when stratified by HLA mismatch. Median survival times and their 95% CIs were, for 0 mismatches, 24.8 (19.9, NA); 1 mismatch, 19.6 (18.3, NA); 2 mismatches, 18.3 (16.3-21.0); 3 mismatches, 14.7 (13.9-15.4); 4 mismatches, 12.5 (11.6-13.7); 5 mismatches, 12.5 (11.6-13.2); and for 6 mismatches, 12.2 (11.1, 13.4). The log rank statistic for equality over strata was 200.8 with 6 *df* ($P < 0.0001$).

Linearity of the HRs in Pediatric Allografts

To assess the strength of the effects of HLA mismatches on pediatric kidney graft failure, a weighted linear regression was performed for each vector of HRs for the reduced and full Cox models for all pediatric kidney transplants and stratified by donor source (**Figures S3-S5, SDC,** http://links.lww.com/TXD/A109, http://links.lww.com/TXD/A111). The slopes of the lines compare the 2 models, the steeper the slope, the stronger the effect of HLA mismatch. Each of the 6 fitted lines in the figures had a statistically significant intercept and slope. In addition, the 95% CIs for the slopes overlapped for the reduced and fully adjusted models in each figure. Therefore, each additional unit of HLA mismatch had the same increasing effect on kidney graft survival, whereas the additional covariates in the full model did not significantly reduce the effects of HLA mismatch.

Figure 4 presents a plot of the regression line and observed HRs for the fully adjusted Cox models for the deceased and living donors. For the living donor stratum, the slope is 0.32, whereas for deceased donors, it is only 0.07. Therefore, the effect of mismatching a living donor kidney is more than 4 times as great on kidney survival as for an organ from

TABLE 2.

Full-model HRs for risk of allograft failure by HLA mismatch with 0 mismatch as the reference among pediatric (age <18 years), first kidney only transplant recipients[a, b, c]

	All donors[a]				Living donors[b]				Deceased donors[c]			
HLA mismatch	N	HR	95% CI	P	N	HR	95% CI	P	N	HR	95% CI	P
0	623	1.00	Reference		402	1.00	Reference		221	1.00	Reference	
1	1010	1.30	1.06-1.58	0.0109	885	1.48	1.15-1.90	0.0022	125	1.16	0.79-1.71	NS
2	3131	1.48	1.24-1.76	<0.0001	2734	1.67	1.33-2.09	<0.0001	397	1.49	1.11-2.00	0.0088
3	4999	1.78	1.50-2.11	<0.0001	3737	2.07	1.66-2.59	<0.0001	1262	1.54	1.18-2.02	0.0018
4	3252	1.85	1.54-2.20	<0.0001	471	2.73	2.10-3.57	<0.0001	2781	1.50	1.15-1.95	0.0028
5	3706	1.99	1.66-2.38	<0.0001	429	3.01	2.27-3.99	<0.0001	3277	1.62	1.25-2.11	0.0003
6	1881	1.92	1.59-2.32	<0.0001	230	2.14	1.51-3.04	<0.0001	1651	1.62	1.23-2.13	0.0005

[a] For all donors: adjustment for recipient age, recipient sex, donor sex, transplant era, recipient ethnicity, donor source, underlying disease, induction, and immunosuppression at discharge.

[b] For living donor model: adjustment for recipient age, donor age, transplant era, recipient ethnicity, underlying disease, induction, and immunosuppression at discharge.

[c] For the deceased donor model: adjustment for recipient age, recipient sex, transplant era, recipient ethnicity, underlying disease, and immunosuppression at discharge.

a deceased donor, when controlled for the covariates in the full models.

Median Survival and HRs by Quartile of Age Show Significant Survival Advantage With Younger Age at Transplant

To study the effect of age of the recipient on kidney survival, an unadjusted KM analysis was performed when stratified by quartile of age (Table 1, Figure 5). Median survival time for Q1 was 18.8 years with 95% CI (17.7-19.9). For Q2, median survival was 14.6 (95% CI, 13.6-15.8), Q3, 12.6 (95% CI, 11.6-13.7), and for Q4, 10.6 years (95% CI, 9.8-11.5 years). The log rank statistic for equality over strata was 382.0 (3 *df*), $P < 0.0001$. A weighted regression line was fitted to the median survival statistics by quartile with an intercept of 20.9 (95% CI, 16.5-25.3; $P = 0.0024$) and slope of −2.69 (95% CI, −4.33 to −1.06; $P = 0.0193$) (Figure 6A). Quartile of recipient age was included in the fully adjusted Cox regression for all pediatric transplants with respective values, Q1-Q4, 1.00, 1.28, 1.55, and 1.76 (Table 5). A weighted regression line was fitted to the HRs with an intercept of 0.76 (95% CI, 0.63-0.89; $P = 0.0016$) and a slope of 0.26 (95% CI, 0.21-0.31; $P = 0.0027$) (Figure 6B). Therefore, survival decreases by 2.69 years for each quartile of recipient age, whereas the hazard of failure increases by 0.26 hazard units for each quartile, when estimated from the fully adjusted model.

DISCUSSION

Improving Survival of Pediatric First Kidney Allografts From 1987 to 2016

To control for the long duration of the database in our Cox multivariate regressions, we included a categorical variable for the era of the transplant (Tables 1, 5). When compared with the reference, years 1987 to 1992, there has been a progressive increase in the survival of children's first kidney allografts when controlled for covariates that include HLA mismatch. Era 1993 to 1997 has an HR of 0.77, followed by subsequent periods and respective HRs of 0.64, 0.56, 0.35, and 0.21, each with a P value less than 0.0001 (Table 5). This is testimony to the improvements in surgical techniques, immunosuppression, and postsurgery clinical treatment in the United States. Despite this good news, HLA mismatch is still a strong risk factor for decreased allograft survival with a 30% reduction for 1 HLA mismatch and almost twofold reduction for 6 mismatches (Table 2).

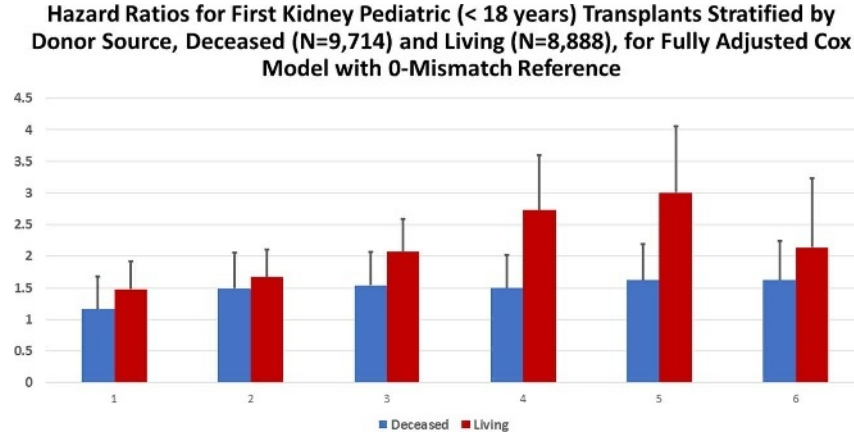

FIGURE 2. A bar graph emphasizes the differences in the HRs of Cox multivariate, fully adjusted models, with HLA mismatch as the primary explanatory variable, for deceased (blue bars) and living (red bars) donors in 18 602 first kidney pediatric (<18 years) transplants (Table 2). For each mismatch category, the HR for the living donor data was larger than for the deceased donor stratum. For mismatches 4 and 5, the 95% CIs exclude one another.

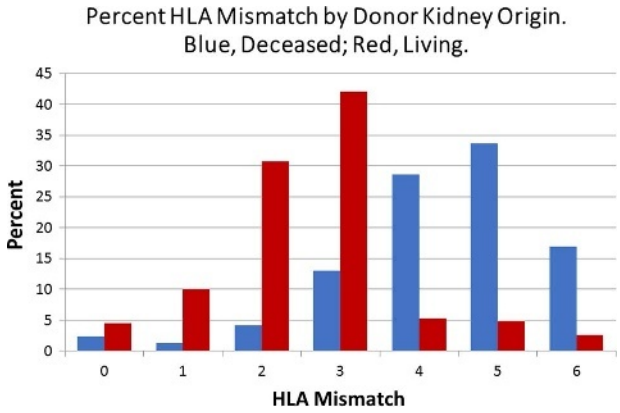

FIGURE 3. The percent HLA mismatch for deceased as compared with living donors is presented. The predominance of "good" mismatches, 0 to 3, in the living donor stratum was the result of these being primarily living-related organs (Table 2). Despite the large differences in mismatch categories 4 to 6, in which the deceased donors have a much higher proportion of mismatches, the respective HRs for the living donors in these categories is always larger in the fully adjusted Cox proportional hazard regression (Table 2).

Comparison of Reduced and Full Cox Models Reveals Role of Covariates

Each set of HRs for the reduced and full models has a significant linear fit (Table S3, http://links.lww.com/TXD/A114 Table 2). These lines can be used to assess the effects of the additional covariates in the full Cox model when compared with the reduced model. The reduced model controls only for recipient age, sex, and era, whereas the full model includes the additional covariates, which include antibody induction therapy and immunosuppression. The slope of the line is a measure of the strength of the decrease in first kidney graft survival as a function of HLA mismatch, the steeper the slope the stronger the effect. Comparing the slopes of the reduced and full models, and the 95% CIs for the HRs, allows us to compare the moderating effect of the covariates on HLA mismatch. For all transplants (**Figure S3, SDC,** http://links.lww.com/TXD/A109) the slope of the reduced model (0.31; 95% CI, 0.22-0.40) is more than twice that for the full one (0.15; 95% CI, 0.07-0.22), though their confidence limits slightly overlap. At each HR, the 95% CIs for the fitted lines overlap. The benefit of the additional covariates can be seen primarily in mismatches 3 to 6. A similar pattern is seen in the lines for the deceased donor stratum (**Figure S4, SDC,** http://links.lww.com/TXD/A110). The similarity of the lines is especially marked in the living donor stratum in which the slopes are identical (0.32), whereas the observed HRs for the 2 models lie close together in the graph at each mismatch value (**Figure S5, SDC,** http://links.lww.com/TXD/A111). In each graph, the moderating effects on graft survival, of adding the additional variables in the full model, are minimal.

This is also true when the HLA-A, -B, and -DRB1 triples are introduced into the reduced and full Cox models (Table 4). Although there is a trend that the HRs in the full model are less than those in the reduced one for the higher mismatch categories 3 to 6, each permutation that is a statistically significant risk in the reduced regression is also significant in the full model. Although HLA mismatching is a risk factor for graft failure, the within category tests of the triples (**Table S5, SDC,** http://links.lww.com/TXD/A116) suggest that each of the loci contributes equally and that DRB1, contrary to common belief, does not play the largest role. This conclusion is also reinforced by the linear relation of the HRs in Table 2 and recent studies in the literature that addressed pediatric renal transplantation and the role of HLA-DRB1.[18-21] We also found this in adult kidney allografts from deceased and living donors.[2,3]

We understand that our finding on the lack of priority for the effect of HLA-DR goes against the long-held opinion in the kidney transplant community and we are humbled and cautious thereby. As an example, it contradicts an earlier finding in a study of kidney transplantation in minority groups that helps illustrate the differences in our approach from that which has commonly been used.[22] First, the Cox model in the cited report was not controlled for induction or immunosuppression at discharge. Further, the models did not adequately control for the correlation between mismatch classes. There are 2 sources of correlation, across loci and within mismatch category. Across loci, when coded as 0, 1, and 2, there are $3\times3\times3 = 27$ permutations of A, B, DR mismatch. When one considers each permutation separately, then the correlation is removed. We also know that across mismatch categories, there is a difference in the hazard of survival. What we need to test is the within mismatch categories for the 27 permutations in categories 1 to 5, of which there are 57 combinations or tests (**Table S5, SDC,** http://links.lww.com/TXD/A116). This removes the within category correlation of mismatch. Then adjust for the total number of tests. We believe this accounts for the difference in our results. Further, evidence that each mismatch is the same comes from our fitting linear regressions to the HRs for the reduced and full models. If indeed HLA-DRB1 played a much larger role, then one would not expect such a uniform relationship. However, each increasing mismatch, irrespective of locus, has the same increment of increase in HR (**Figures S3-S5, SDC,** http://links.lww.com/TXD/A109, http://links.lww.com/TXD/A111). How does one explain this other than that the mismatches within each category are the same, which we show with our tests?

Impact of HLA Mismatch in Children Mirrors That in Adults for Living Donor Organs

Although living organs, from donors of all ages, had a longer unadjusted median survival in K-M analysis, the penalty in survival for HLA mismatching a living organ in the higher mismatch categories is greater, as we also demonstrated in an earlier paper in first kidney transplants in adults (≥18 years).[3] In Figure 2, the HR in each category of mismatch is greater

TABLE 3.

Full-model HRs for risk of allograft failure by HLA mismatch with deceased donor, 0 to 3 mismatches, as the reference among pediatric (age <18 years), first kidney only transplant recipients[a]

HLA mismatch	N	HR	95% CI	P
Deceased donor, 0-3 HLA mismatches	2005	1.00	Reference	
Deceased donor, 4-6 HLA mismatches	7709	1.08	0.99-1.18	0.0688
Living donor, 0-3 HLA mismatches	7758	0.68	0.63-0.74	<0.0001
Living donor, 4-6 HLA mismatches	1130	1.03	0.90-1.17	NS

[a] Adjustment for recipient age, recipient sex, donor sex, transplant era, recipient ethnicity, underlying disease, induction, and immunosuppression at discharge.

TABLE 4.

HR for risk of allograft failure for HLA mismatch triple with [0, 0, 0] as the reference among pediatric (age < 18 y), first kidney-only transplant recipients

			Reduced model[a]			Full model[b]		
Mismatch category	Triple [A, B, DR]	N	HR	95% CI	*P*	HR	95% CI	*P*
0	[0, 0, 0]	623	1.00	Reference		1.00	Reference	
1	[0, 0, 1]	324	1.19	0.92-1.54	N/S	1.24	0.96-1.61	NS
1	[0, 1, 0]	409	1.35	1.06-1.71	0.0144	1.37	1.08-1.74	0.0105
1	[1, 0, 0]	277	1.12	0.83-1.49	NS	1.22	0.91-1.64	NS
2	[0, 0, 2]	24	1.49	0.76-2.92	NS	1.38	0.70-2.71	NS
2	[0, 1, 1]	1279	1.46	1.20-1.76	0.0001	1.51	1.25-1.83	<0.0001
2	[0, 2, 0]	37	1.36	0.74-2.52	NS	1.21	0.65-2.24	NS
2	[1, 0, 1]	576	1.42	1.14-1.76	0.0018	1.42	1.14-1.77	0.0016
2	[1, 1, 0]	1195	1.40	1.16-1.67	0.0006	1.45	1.20-1.76	0.0002
2	[2, 0, 0]	20	2.64	1.49-4.65	0.0008	2.00	1.13-3.54	0.0176
3	[0, 1, 2]	121	2.16	1.56-2.97	<0.0001	1.87	1.35-2.59	0.0002
3	[0, 2, 1]	214	2.83	2.15-3.73	<0.0001	2.45	1.86-3.24	<0.0001
3	[1, 0, 2]	32	2.76	1.62-4.71	0.0002	2.29	1.34-3.91	0.0025
3	[1, 1, 1]	4223	1.69	1.42-2.00	<0.0001	1.72	1.45-2.05	<0.0001
3	[1, 2, 0]	216	2.74	2.09-3.59	<0.0001	2.37	1.80-3.12	<0.0001
3	[2, 0, 1]	56	1.44	0.86-2.42	NS	1.24	0.74-2.09	NS
3	[2, 1, 0]	137	2.24	1.64-3.05	<0.0001	1.80	1.31-2.46	0.0003
4	[0, 2, 2]	194	2.61	1.93-3.52	<0.0001	2.13	1.57-2.89	<0.0001
4	[1, 1, 2]	637	2.11	1.71-2.61	<0.0001	1.76	1.42-2.19	<0.0001
4	[1, 2, 1]	1335	2.25	1.87-2.72	<0.0001	1.88	1.55-2.29	<0.0001
4	[2, 0, 2]	48	3.36	2.14-5.26	<0.0001	2.55	1.62-4.01	<0.0001
4	[2, 1, 1]	768	2.37	1.94-2.89	<0.0001	1.91	1.56-2.35	<0.0001
4	[2, 2, 0]	270	2.45	1.90-3.14	<0.0001	1.81	1.40-2.34	<0.0001
5	[1, 2, 2]	1405	2.56	2.12-3.09	<0.0001	2.11	1.74-2.57	<0.0001
5	[2, 1, 2]	629	2.79	2.26-3.45	<0.0001	2.18	1.75-2.71	<0.0001
5	[2, 2, 1]	1672	2.44	2.03-2.93	<0.0001	1.92	1.59-2.32	<0.0001
6	[2, 2, 2]	1881	2.53	2.11-3.04	<0.0001	1.96	1.62-2.37	<0.0001

[a] Adjustment for recipient age, recipient sex, and transplant era.

[b] Adjustment for recipient age, recipient sex, donor sex, transplant era, recipient ethnicity, donor source, underlying disease, induction, and immunosuppression at discharge.

for the living stratum than for the deceased. For mismatch categories 4 and 5, the CIs exclude one another. We fitted a line through the full model HRs for pediatric kidneys (Table 2) of the living donor stratum and compared it with the one in the deceased donor group (Figure 4). The slope of the living donor line was 0.32 (95% CI, 0.14-0.50; $P = 0.0055$) compared with 0.07 (95% CI, 0.02-0.13; $P = 0.0208$) for the deceased stratum. This demonstrates that the increased, linear, increment of risk for kidney failure for living donor organs was more than 4 times the magnitude of that for deceased donors when mismatching pediatric kidneys, when controlled for all covariates in the full Cox model and despite the overall better survival of living donor organs. This is especially surprising in the light of the mismatch distribution in Figure 3 in which deceased organs represent the largest proportions of HLA mismatches in categories 4 to 6. One possibility is that the mismatched HLA of living donor kidneys present a better target for the immune system of the recipient than those on the organ of the deceased donor, possibly related to subliminal damage and exposure of target structure for immunological attack due to pretransplant ischemic preservation. The very low slope of the deceased donor line, and its marginal statistical significance, suggests that the effect of each additional HLA mismatch is minimal for allograft survival. Therefore, deceased donor kidneys might be a better choice, from the HLA perspective, in these higher mismatch categories.

A Well-matched Allograft From a Deceased Person Is Equivalent or Better in Survival to One From a Poorly Matched Living Donor

We explored this question further in Table 3 where we found that organs from deceased donors with 0 to 3 mismatches were equivalent in survival with those from living donors with 4 to 6 mismatches. In pediatric transplants recorded by the Collaborative Transplant Study from 2000 to 2015, it was reported that 10-year allograft survival from living donors who were mismatched 4 to 6 for HLA-A, -B, and -DR was significantly worse than for patients with allografts from deceased donors who were matched as either 0 or 1.[23] In the present study, there were only 346 children who received an allograft from a deceased person with 0 or 1 mismatch. When we ran a fully adjusted Cox model with deceased donors with 0 or 1 mismatch as a reference, living donors with 4 to 6 mismatches also had worse survival, with HR of 1.36 (95% CI, 1.09-1.69; $P = 0.0066$). The situation in which a clinician has a choice between a well-matched organ from a deceased donor and a poorly matched one from a living donor is rare. However, when it occurs, one must consider the "matchability" of the recipient with a deceased donor and the

TABLE 5.

Covariate results for full Cox regression model with HLA mismatch as the primary explanatory variable for all first pediatric kidney allografts

Variables	Reference	HR	95% CI	*P*
Recipient age, y	Quartile 1			
Quartile 2		1.28	1.18-1.38	<0.0001
Quartile 3		1.55	1.44-1.67	<0.0001
Quartile 4		1.76	1.63-1.90	<0.0001
Recipient sex	Male	1.14	1.08-1.21	<0.0001
Donor sex	Male	1.07	1.02-1.13	0.0083
Transplant era	1987-1992			
1993-1997		0.77	0.71-0.84	<0.0001
1998-2002		0.64	0.57-0.72	<0.0001
2003-2007		0.56	0.49-0.64	<0.0001
2008-2012		0.35	0.30-0.40	<0.0001
2013-2016		0.21	0.17-0.27	<0.0001
Ethnicity	Non-Hispanic whites			
Hispanic		1.11	1.03-1.20	0.0084
Asians		0.75	0.62-0.90	0.0019
Blacks		1.77	1.65-1.89	<0.0001
American Indians		1.19	0.92-1.54	NS
Pacific Islanders		1.43	0.98-2.08	NS
Donor type	Deceased			
Living		0.77	0.72-0.83	<0.0001
Underlying disease	Congenital dysplasia			
Focal glomerular sclerosis		1.42	1.27-1.58	<0.0001
Congenital obstructive uropathy		1.07	0.95-1.21	NS
Chronic glomerulonephritis unspecified		1.24	1.10-1.40	0.0004
Chronic pyelonephritis/reflux nephropathy		1.29	1.11-1.49	0.0007
Polycystic kidneys		1.27	1.09-1.49	0.0028
Acquired obstructive nephropathy		1.13	0.98-1.31	NS
Hemolytic uremic syndrome		1.17	0.97-1.42	NS
Alport syndrome		1.01	0.84-1.22	NS
Prune belly syndrome		1.18	0.97-1.44	NS
IGA nephropathy		1.47	1.21-1.78	0.0001
Systemic lupus erythematosus		1.50	1.25-1.81	<0.0001
Other diseases/states		1.19	1.09-1.30	0.0002
Not reported		1.09	0.92-1.29	NS

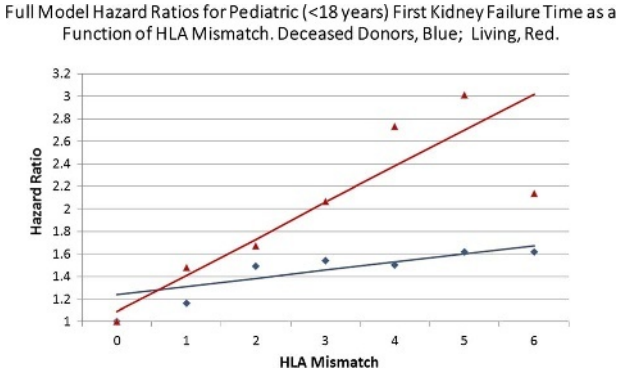

FIGURE 4. Weighted linear regressions were performed for the fully adjusted Cox multivariate regression HRs for the deceased and living donors for all pediatric transplants in the UNOS STAR data set, 1987–2016 (Table 2). The relative slopes of the lines can be used to graphically compare the strength of the HLA mismatches in the failure of pediatric transplants. The slope of the living donor line was more than 4 times larger, 0.32 (0.14-0.50; $P = 0.0055$) compared with 0.07 (0.02-0.13; $P = 0.0208$) for the deceased stratum.

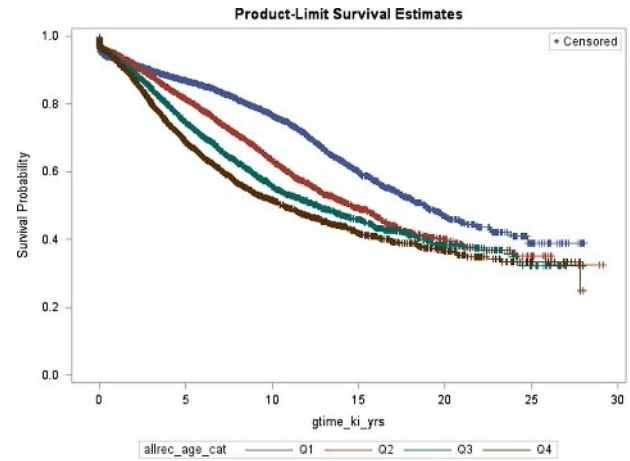

FIGURE 5. An unadjusted KM analysis was performed for 18 602 pediatric transplants from the UNOS STAR data files from 1987 to 2016 when stratified by quartile of age. Survival was significantly related to quartile with Q1 > Q2 > Q3 > Q4. The log-rank test statistic for equality over strata is 382.0 with 3 *df* ($P < 0.0001$).

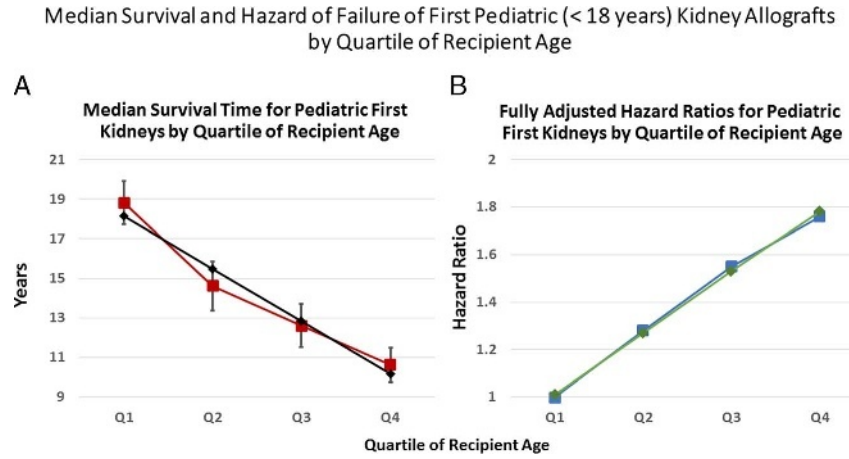

FIGURE 6. A, Weighted linear regression (black line) performed with the median survival times from KM curves (red squares) for all pediatric transplants when stratified by quartile of age at transplant. The line has a slope of –2.69 (–4.33 to –1.06), $P = 0.0193$. Therefore, kidney survival time decreases at a rate of 2.7 years per quartile of increasing age. B, Weighted linear regression (green line) of the fully adjusted HRs from a Cox proportional hazards analysis (blue squares) by quartile of recipient age (Table 5). The slope of the line is 0.26 (0.21-0.31), $P = 0.0020$. The hazard of pediatric kidney failure increases by 0.26 hazard unit per quartile of recipient age. Our hypothesis is that this reflects the loss of immunological malleability as the children become older.

position of the living donor. Matchability has been defined as the percent chance that the recipient would receive an allograft with 0 or 1 mismatch out of 1000 kidney donors.[24] If this number were a high predictive score for a 0 or 1 mismatch, then the waiting time for an organ might be short, and it might behoove the patient and surgeon to wait for a deceased donor organ. Otherwise, the poorly matched living organ would be chosen. However, for the living donor, such a choice has consequences: major surgery, removal of a vital organ, personal inconvenience, additional costs, hospital resources, and clinical time. The choice must balance the matchability of a deceased organ and waiting time with the implications for the living donor for an allograft with statistically poorer or same likelihood of survival.

Age Effect on Pediatric Kidney Graft Survival

When an unadjusted KM curve is fitted to first pediatric kidney survival, when stratified by quartile of age, there is an inverse relation in the survival of the organ with age (Figure 5). This is best demonstrated in Figure 6A, in which a line is fitted to the median survival times, where the negative slope is –2.69 years per quartile of child age, and the 95% CIs of the median survival estimates overlap the line. When this line is compared with that fitted through the full model Cox HRs of the quartiles of age in Table 5 and Figure 6B, the slope is now positive, 0.25 hazard units per quartile of age increase in the risk of kidney graft failure, whereas the observed HRs are nearly coextensive with the predicted points in the line.

A study of 18 310 persons who were transplanted younger than 21 years demonstrated an increase in the risk of kidney failure in teenagers and defined a high-risk window for failure for 17 years or older and younger than 24 years.[8] One explanation for these changes is that patient adherence to their medical regimen changes with time, such that as the children age, the side effects that the immunosuppressive therapy imposes on their physiology, sexual and hormonal maturation, and lifestyle cause them to be less compliant.[9,25,26] Other suggested mechanisms are differences in insurance coverage and transitions from pediatric to adult healthcare.[9] However, these would not explain the best survival of transplants in the youngest recipients in the first quartile. Moreover, if nonadherence with the prescribed medical regimen was the significant contributor to decreased graft survival, it would be expected that these youngest recipients at time of transplantation would also be affected as they reached their teens. Instead, in our data, their unadjusted KM line lies on top and separate from the other 3 lines in Figure 5. Further, for the first 15 years of the graph, the survival has the ordered relation Q1 > Q2 > Q3 > Q4, a pattern which would be difficult to explain by decreased adherence alone, where one would expect to have greater variation.

It may be that the distinct graft survival advantage in children transplanted at younger ages is a reflection of their having experienced fewer cumulative years of the damaging systemic effects of kidney failure. However, we offer an alternate hypothesis, the loss of immunological malleability with increasing age at transplant, that might work in tandem with these other mechanisms. Under this hypothesis, the high-risk window would reflect the peak of the immunological maturation curve. Infants and very young children are not entirely immunocompetent, having mostly naive phenotype immune cells and a paucity of immunologic memory, which, together with deficiencies in costimulatory molecules and cytokine pathways results in decreased capacity to respond effectively to immune stimuli.[27] Moreover, as originally described by Billingham et al,[28] susceptibility to tolerance induction to foreign antigens is known to be highest during early life and decreases with age. This is strongly suggested by the pattern of immune development after ABO-incompatible heart transplantation in young children that has greatly increased their donor pool.[29,30] These children spontaneously develop donor-specific B cell tolerance, failing to produce the normal, naturally-occurring antibodies to the non-self ABO antigen(s) of their donor organ.[31,32] Further, survival after pediatric heart transplantation reflects a similar, also highly significant trend in which patients transplanted as infants have the longest median survival of 20.7 years (compared with 18.2 years for children aged

1-5 years, 14.0 years for aged 6-10 years, and 12.7 years for recipients aged 11–17 years), and generally require less immunosuppressive therapy even during their adolescent years.[33]

Our hypothesis is that immunologic malleability or plasticity, allowing an immune response to nonself antigens that are continuously present (ie, in the graft) to become muted rather than augmented, is a function of age and is essentially lost in the adult. There is undoubtedly a complex set of factors underlying such a phenomenon involving many components of the immune system that mature with age, likely including T cells, B cells, NK cells, and their coreceptors. One possible mechanism to explain this superior survival when transplantation is performed in very young children is the low proportion of $CD27^+$ "memory" B cells in infants.[34] A second potential mechanism is the role of the B cell coreceptor CD22, an inhibitory molecule that, when engaging its ligand CD22L, inactivates or turns off B cells when the B-cell receptor engages its cognate antigen.[35] Infant B cells express CD22 at higher levels than B cells from older children. This trend of decreasing CD22 expression with age could partially contribute to less aggressive responses to graft antigens, even of immune malleability leading to tolerance, and is one of a number of elements of immaturity that could be exploited to achieve better outcomes in pediatric transplantation.

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