Human leukocyte antigen mismatching and survival after lung transplantation in adult and pediatric patients with cystic fibrosis

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ABSTRACT

Introduction: The influence of human leukocyte antigen (HLA) mismatching on survival in adult and pediatric patients with cystic fibrosis (CF) after lung transplantation (LTx) is unknown.

Methods: The United Network for Organ Sharing database was queried from 1987 to 2013 to determine the influence of HLA mismatching on survival in adult and pediatric CF LTx recipients by assessing the association of HLA mismatching with survival in first-time adult (aged ≥ 18 years) and pediatric (aged <18 years) recipients.

Results: Of 3149 adult and 489 pediatric patients with CF, 3145 and 489 were used for univariate Cox analysis, 2687 and 363 for Kaplan-Meier survival analysis, and 2073 and 257 for multivariate Cox analysis, respectively. Univariate analyses in adult and pediatric patients with CF demonstrated conflicting associations between HLA mismatching and survival (adult hazard ratio [HR], 1.0; 95% confidence interval [CI], 0.97-1.1; $P = .45$ vs pediatric HR, 0.87; 95% CI, 0.77-0.99; $P = .032$). Multivariate Cox models including both pediatric and adult patients confirmed that HLA mismatching had an initially protective effect at young ages (HR, 0.85; 95% CI, 0.73-0.99; $P = .044$) and that this protective effect diminished at older ages and was no longer associated with survival at $P < .05$ beyond age 10 years.

Conclusions: HLA mismatching has significantly different implications for survival after LTx in adult compared with pediatric patients with CF. (J Thorac Cardiovasc Surg 2016;151:549-57)

Kaplan-Meier survival functions for children with cystic fibrosis by human leukocyte antigen mismatch.

Central Message

Human leukocyte antigen mismatching has a protective effect in young patients with cystic fibrosis with loss of this effect beyond age 10 years.

Perspective

The present study provides some insight into what appears to be immunologic distinctions according to age in adult and pediatric lung transplant recipients with cystic fibrosis. Further research is needed to better define the influence of humoral immunity on age-related survival disparities in this patient population.

See Editorial Commentary page 558.

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Lung transplantation (LTx) has become a well-established treatment option for both adult and pediatric patients who have cystic fibrosis (CF) with advanced lung disease.^{1,2} A

recent analysis of the United Network for Organ Sharing (UNOS) registry examining patients between 2005 and 2009 after implementation of the lung allocation score (LAS) demonstrated a survival benefit for adults with CF.³ However, the long-term benefit of LTx in children with CF has been widely debated and remains controversial.⁴⁻⁶ In 2007, Liou and colleagues⁴ published that 5 of 514 wait-listed patients had improved survival through proportional-hazards modeling of wait-listed pediatric

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Received for publication Feb 26, 2015; revisions received Aug 3, 2015; accepted for publication Aug 10, 2015; available ahead of print Sept 20, 2015.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2015.08.022>

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Abbreviations and Acronyms

AMR	=	antibody-mediated rejection
BOS	=	bronchiolitis obliterans syndrome
CF	=	cystic fibrosis
DSA	=	donor-specific anti-HLA antibody
HLA	=	human leukocyte antigen
LAS	=	lung allocation score
LTx	=	Lung transplantation
UNOS	=	United Network for Organ Sharing

patients with CF who underwent LTx between 1992 and 2002.⁴ Subsequent criticisms of these findings included the use of registry data not being updated at the time of LTx with covariates being acquired up to 2 years before listing, which equated to ≥ 3 years before LTx, and the use of a cohort of patients before the implementation of the LAS system in the United States.^{5,6}

Using piecewise-constant hazard rate, our group recently reported that the hazard of post-LTx mortality in CF is highest between ages 16 and 20 years, but this risk declined at later attained ages, controlling for age at LTx and other donor, recipient, and transplant characteristics.⁷ Due to the study design of that analysis, we could not determine any factors contributing to the death of adolescent CF patients after LTx. Given that the age at time of LTx in adolescents with CF negatively influenced survival but not for adult CF patients,⁷ we sought to investigate immunologic differences as potential factors contributing to the disparities seen in the adult and pediatric CF patient populations. With no data available regarding human leukocyte antigen (HLA) mismatching in CF patients receiving LTx, we used the UNOS Registry to analyze HLA mismatching in both adult and pediatric CF patient groups. We hypothesized that HLA mismatching negatively influences long-term outcomes of LTx in both CF age groups.

METHODS**Data Collection**

We retrospectively evaluated data from patients who were registered in the Organ Procurement and Transplant Network Standard Transplant Analysis and Research Database⁸ administered by UNOS. The study was approved by The Ohio State University Wexner Medical Center Institutional Review Board with a waiver of the need for individual consent (IRB#2012H0306). The UNOS/Organ Procurement and Transplant Network thoracic database was queried for all patients with CF between October 1987 and September 2013 who received first-time, cadaveric LTx with known transplant date and were not duplicate entries. A total of 3149 adult patients with CF (aged ≥ 18 years) and 489 pediatric patients with CF (younger than age 18 years) were included in the analysis.

Statistical Methods

All analyses were performed using Stata/MP, version 13.1 (StataCorp LP, College Station, Tex). Descriptive statistics for continuous variables are presented as means and standard deviations; and descriptive statistics for categorical variables are presented as proportions. Survival analysis was performed on time from LTx to the date of death. There were 4 adult patients with CF with

unknown time spent at risk, and these were excluded from the survival analysis. Eighteen patients had 0 days at risk, of whom 17 died due to the following causes: intraoperative hemorrhage (7 cases), infection (4 cases), and other causes (6 cases). Patients with 0 days at risk were assigned an arbitrarily small duration at risk < 1 day to be retained in the survival analysis. Whereas the present analysis focused on patient survival, hospitalization due to infection, and the development of posttransplant bronchiolitis obliterans syndrome (BOS) within a year of LTx were also described as secondary outcomes.

The main covariates of interest were HLA mismatch level (dichotomized as ≥ 3 vs 0-2 in descriptive and Kaplan-Meier analyses, but treated as continuous in the regression analysis) at time of listing for LTx with a total of 6 being possible with the loci, including A, B, and DR. The level of mismatch used to illustrate differences in survival curves and patient characteristics was arbitrarily chosen. Cox proportional hazards analysis related HLA mismatch to survival after LTx separately in adults and children, and in the combined sample with continuous age as a moderator of this relationship. Multivariate Cox proportional hazards analysis adjusted for recipient characteristics, donor characteristics, and transplant characteristics. The sample for the multivariate analysis was constructed from cases with complete data on all covariates. Six-minute walk distance was not included in the multivariate models due to the high proportion of missing data and the fact that this variable was only collected from 2001 to 2006. The final LAS was only available for patients transplanted in May 2005 or later, and this variable was only considered as a covariate in separate models fitted to the 2005 to 2013 subsample.

RESULTS**Study Population**

Tables 1 and 2 summarize demographic information and characteristics of the adult and pediatric patients using the HLA mismatch ≥ 3 threshold to illustrate differences across HLA mismatch level. In the adult CF population (Table 1), the 2 groups divided by HLA mismatch level were similar in recipient and donor sex, recipient race, and other recipient characteristics (eg, infection requiring intravenous drug therapy during the 2 weeks before LTx, age, creatinine, body mass index, pulmonary function, functional capacity, and final LAS) and transplant characteristics (transplant year and graft ischemic time). However, the HLA ≥ 3 mismatch group had significantly more adult CF patients who received allografts from nonwhite donors. A comparison across the same threshold of HLA mismatch in the pediatric CF population (Table 2) also revealed similarity across the same characteristics, with the exception of infection before LTx, which was more common in the HLA ≥ 3 mismatch group.

In the adult subsample, 472 patients (22%) were hospitalized for infection within a year of LTx, whereas 59 (2%) developed BOS within the same time span. In the pediatric subsample, there were 84 patients (22%) hospitalized for infection within 1 year, and 18 (4%) who developed BOS within 1 year of LTx. A comparison of continuous HLA mismatch level between patients who were not hospitalized for infection and those who were not found no significant differences among either children ($P = .78$) or adults ($P = .99$). Likewise, patients who developed BOS were not distinguished from patients who did not develop BOS in their level of HLA mismatch among either children ($P = .90$) or adults ($P = .50$). These

TABLE 1. Patient demographic information and characteristics of adults with cystic fibrosis according to human leukocyte antigen (HLA) mismatch ≥ 3 versus 0 to 2

Variable	Missing data	All* (n = 3149)		HLA ≥ 3 (n = 2599)		HLA 0-2 (n = 91)		P value	
		n (%)	Mean $\pm$ SD	n (%)	Mean $\pm$ SD	n (%)	Mean $\pm$ SD	t test	χ^2
Male recipient	0	1716 (54)	—	1395 (54)	—	56 (62)	—	—	.14
Male donor	0	1813 (58)	—	1505 (58)	—	50 (55)	—	—	.57
Race of recipient	0	—	—	—	—	—	—	—	.54
White	—	3034 (96)	—	2505 (96)	—	88 (97)	—	—	—
Black	—	36 (1.1)	—	29 (1.1)	—	0	—	—	—
Other	—	79 (2.5)	—	65 (2.5)	—	3 (3.3)	—	—	—
Race of donor	0	—	—	—	—	—	—	—	<.001
White	—	2120 (67)	—	1721 (66)	—	80 (88)	—	—	—
Black	—	517 (16)	—	448 (17)	—	5 (5.5)	—	—	—
Other	—	512 (16)	—	430 (17)	—	6 (6.6)	—	—	—
Infection before lung transplant	384	1238 (45)	—	1019 (45)	—	29 (37)	—	—	.15
Age (y)	0	—	31 (9.1)	—	31 (9.2)	—	32 (9.4)	.16	—
Transplant year	0	—	2004 (6.2)	—	2004 (6.2)	—	2003 (6.1)	.45	—
Creatinine (mg/dL)	248	—	0.78 (0.55)	—	0.78 (0.52)	—	0.81 (0.33)	.58	—
Body mass index	3	—	19 (2.9)	—	19 (2.9)	—	19 (2.8)	.93	—
Ischemic time (h)	251	—	5.8 (1.7)	—	5.8 (1.7)	—	5.9 (1.6)	.58	—
Forced expiratory volume in 1 s (% predicted)	261	—	26 (14)	—	26 (13)	—	25 (15)	.72	—
Forced vital capacity (% predicted)	252	—	41 (14)	—	41 (14)	—	40 (14)	.73	—
6-Mintue walk test (100 ft)	2860	—	10 (5.3)	—	10 (5.2)	—	11 (3.0)	.68	—
Lung allocation score	1621	—	47 (16)	—	47 (16)	—	47 (16)	.90	—
HLA mismatch	459	—	4.6 (1.1)	—	4.7 (0.95)	—	1.7 (0.53)	<.001	—

HLA, Human leukocyte antigen; SD, standard deviation. *A total of 2690 cases had data on HLA mismatch.

secondary outcomes appeared to be unrelated to a continuous measure of HLA mismatch in this study.

Univariate and Kaplan-Meier Survival Analysis

The univariate Cox proportional hazards analysis revealed conflicting results for adult compared with pediatric CF patients (Tables 3 and 4). In patients aged ≥ 18 years, a continuous measure of HLA mismatch was not statistically significantly associated with survival, with a hazard ratio (HR) of 1.0; 95% confidence interval (CI) of 0.97 to 1.1, and $P = .045$ (Table 3). Among patients aged <18 years, on the other hand, the hazard of mortality was reduced for patients with higher levels of HLA mismatch (HR, 0.87; 95% CI, 0.77-0.99; $P = .032$) (Table 4). Adding polynomial (eg, quadratic) transformations of HLA mismatch level did not indicate that the relationship between HLA mismatch and survival was nonlinear among either adults or children (results available upon request). Kaplan-Meier survival function curves comparing HLA ≥ 3 and 0 to 2 mismatch groups in the adult CF population (Figure 1) and pediatric CF population (Figure 2) found similarly conflicting results, with log-rank tests indicating an inverse association between HLA mismatch and mortality hazard among children, but not among adults. Number of patients at risk by HLA mismatch level and year since transplant for both adult and pediatric groups are outlined in Tables E1 and E2.

Several variables were found to be significant in the univariate Cox models for the adult patients with CF (Table 3). Black donor race, among adults receiving a transplant in May 2005 or later, higher final LAS, were significantly associated with increased mortality hazard. Meanwhile, several covariates were protective against death. Older age, higher pulmonary function (forced vital capacity and forced expiratory volume in 1 second), and functional capacity (6-minute walk distance in hundreds of feet) were protective with a decrease in the HR for mortality. A more recent LTx was associated with a lower hazard of death among adults in the univariate analysis. No variables other than HLA mismatch level were significantly associated with mortality in the univariate Cox models for the pediatric patients with CF (Table 4).

Multivariate Survival Analysis

Adjusting for confounders in the subsample of adult patients with CF, multivariate Cox proportional hazard models identified no relation between HLA mismatch level (as a continuous variable) and mortality hazard (HR, 1.0; 95% CI, 0.95-1.1; $P = .68$) (Table 5). Restricting the analysis to transplants performed in May 2005 or later and controlling for final LAS did not change this finding (Table 5, Model 2), whereas LAS itself was not significantly related to the outcome net of the other covariates. Covariates that remained significantly related to mortality among adult

TABLE 2. Patient demographic information and characteristics of children with cystic fibrosis according to human leukocyte antigen (HLA) mismatch ≥ 3 versus 0 to 2

Variable	Missing data	All* (n = 489)		HLA ≥ 3 (n = 342)		HLA 0-2 (n = 21)		P value	
		n (%)	Mean $\pm$ SD	n (%)	Mean $\pm$ SD	n (%)	Mean $\pm$ SD	t test	χ^2
Male recipient	0	191 (39)	—	132 (39)	—	4 (19)	—	—	.072
Male donor	0	248 (51)	—	187 (55)	—	9 (43)	—	—	.29
Race of recipient	0	—	—	—	—	—	—	—	.77
White	—	427 (87)	—	306 (89)	—	19 (90)	—	—	—
Black	—	11 (2.3)	—	8 (2.3)	—	0	—	—	—
Other	—	51 (10.4)	—	28 (8.2)	—	2 (9.5)	—	—	—
Race of donor	0	—	—	—	—	—	—	—	.080
White	—	321 (66)	—	223 (65)	—	18 (86)	—	—	—
Black	—	82 (17)	—	60 (18)	—	0	—	—	—
Other	—	86 (18)	—	59 (17)	—	3 (14)	—	—	—
Infection before lung transplant	63	256 (60)	—	171 (59)	—	5 (31)	—	—	.029
Age (y)	0	—	14 (3.1)	—	14 (3.0)	—	15 (2.3)	.13	—
Transplant year	0	—	2003 (6.2)	—	2002 (6.2)	—	2001 (7.2)	.68	—
Creatinine (mg/dL)	67	—	0.61 (1.1)	—	0.62 (1.2)	—	0.47 (0.18)	.62	—
Body mass index	15	—	17 (2.8)	—	17 (2.8)	—	18 (3.0)	.054	—
Ischemic time (h)	28	—	5.4 (1.4)	—	5.4 (1.5)	—	5.3 (1.4)	.67	—
Forced expiratory volume in 1 s (% predicted)	65	—	30 (14)	—	30 (15)	—	33 (19)	.35	—
Forced vital capacity (% predicted)	62	—	42 (15)	—	43 (15)	—	44 (15)	.68	—
6-Minute walk test (100 ft)	437	—	11 (5.1)	—	10 (4.6)	—	16 (7.2)	.12	—
Lung allocation score	281	—	41 (16)	—	43 (17)	—	41 (7.5)	.79	—
HLA mismatch	126	—	4.6 (1.1)	—	4.7 (0.94)	—	1.9 (0.44)	<.001	—

HLA, Human leukocyte antigen; SD, standard deviation. *A total of 363 cases had data on HLA mismatch.

patients included black donor race being associated with greater hazard of death, and greater forced expiratory volume in 1 second and older age reducing the hazard. Adding polynomial transformations of age (eg, a quadratic term) to the model did not alter the main findings for HLA mismatch (results available upon request).

After adjusting for all confounders among pediatric patients with CF, the multivariate Cox proportional hazard model showed that the continuous measure of HLA mismatch fell short of attaining a statistically significant association with mortality, despite retaining the same magnitude (HR, 0.87; 95% CI, 0.73-1.0; $P = .093$) (Table 6, Model 1). Nevertheless, in the subsample of pediatric patients with CF transplanted in May 2005 or later, and with the addition of a control for final LAS, HLA mismatch remained inversely associated with mortality hazard in the multivariate analysis (HR, 0.71; 95% CI, 0.54-0.93; $P = .015$) (Table 6, Model 2). Covariates significantly associated with greater mortality hazard among all pediatric patients with CF included black recipient race and older age. In comparison, donor race other than black or white was associated with lower mortality hazard.

Conflicting results on the relationship between HLA mismatch level and mortality hazard in the adult and pediatric subsamples suggested that the HR of HLA mismatch was dependent on age at transplantation. Two multivariate Cox proportional hazards models interacting continuous HLA

mismatch with continuous age were fitted in Table 7. Model 3 includes the main effects of HLA mismatch and age, and their interaction, but no additional covariates. This model suggests that at age 0 years, HLA mismatch is inversely related to mortality hazard (HR, 0.87; 95% CI, 0.77-0.99; $P = .030$), but this HR increases as age (scaled by a factor of 10) increases, with the interaction HR being statistically significant and >1 (HR, 1.1; 95% CI, 1.0-1.1; $P = .023$). Thus, Model 3 implies that at age 10 years, the relationship between HLA mismatch and mortality hazard diminishes, but remains statistically significant (HR, 0.90; 95% CI, 0.81-0.99; $P = .036$). This pattern is confirmed after adjusting for all covariates in Model 4, with the interaction between HLA mismatch and age remaining significant and in the same direction as in the unadjusted model (HR, 1.1; 95% CI, 1.0-1.1; $P = .038$).

Both Model 3 and Model 4 imply that at some age, the HR of HLA mismatch will cease to be significantly different from 1. The age threshold below which HLA mismatch was inversely related to mortality hazard at $P < .05$ was 15 years in Model 3 and 10 years in the fully adjusted Model 4. Beyond these respective ages, a continuous measure of HLA mismatch was not significantly related to mortality hazard in the corresponding model. Whereas age was entered as a linear term in Table 7, adding polynomial (eg, quadratic) transformations of age to Models 3 and 4 and interacting the quadratic age terms

TABLE 3. Univariate Cox survival analysis of adults with cystic fibrosis (n = 3145)

Variable	n	Hazard ratio	95% Confidence interval	P value
Human leukocyte antigen mismatch	2687	1.0	0.97-1.1	.45
Male recipient	3145	1.0	0.94-1.1	.49
Male donor	3145	1.0	0.90-1.1	.95
Race of recipient	3145			
White		ref		
Black		1.2	0.76-1.8	.47
Other		0.82	0.58-1.2	.28
Race of donor	3145			
White		ref		
Black		1.2	1.0-1.4	.010
Other		1.1	0.93-1.2	.37
Infection before lung transplant	2765	1.2	1.0-1.3	.009
Age (y)	3145	0.98	0.97-0.98	<.001
Transplant year	3145	0.98	0.97-0.98	<.001
Creatinine (mg/dL)	2901	1.1	0.97-1.2	.16
Body mass index	3142	0.98	0.96-1.0	.082
Ischemic time (h)	2898	0.97	0.94-1.0	.054
Forced expiratory volume in 1 s (% predicted)	2888	0.99	0.99-1.0	.022
Forced vital capacity (% predicted)	2897	0.99	0.99-1.0	.016
6-Minute walk test (100 ft)	289	0.96	0.93-0.99	.012
Lung allocation score	1524	1.0	1.0-1.0	.001

ref, Reference category.

with HLA mismatch did not reveal statistically significant interactions between the square of age and HLA mismatch. This suggested that was the log hazard ratio of HLA mismatch was linearly dependent on age at transplantation (results available upon request).

DISCUSSION

The majority of the medical literature on the influence of HLA mismatching on clinical outcomes after LTx are limited to single-center observations. Although results vary, the generally accepted consensus is that HLA mismatching is detrimental to the survival of patients after LTx.⁹⁻¹⁹ The most important finding of our study is that higher HLA mismatch level lowered the hazard of posttransplant mortality in children with a CF diagnosis, particularly in the youngest segment of this group. Although the small size of the pediatric cohort raises the question of whether this finding was related to chance, statistical analyses demonstrate a significant association adjusting for a variety of recipient, donor, and transplant characteristics, while also explicitly modeling age as a continuous moderator of the HLA mismatch effect.

Cellular immunity after solid organ transplantation involves direct stimulation by dendritic cells in the graft²⁰ or activation of T cells through the migration of

TABLE 4. Univariate Cox survival analysis of children with cystic fibrosis (n = 489)

Variable	n	Hazard ratio	95% Confidence interval	P value
Human leukocyte antigen mismatch	363	0.87	0.77-0.99	.032
Male recipient	489	0.84	0.65-1.1	.19
Male donor	489	0.99	0.78-1.3	.96
Race of recipient	489			
White		ref		
Black		1.1	0.44-2.6	.90
Other		1.0	0.68-1.6	.89
Race of donor	489			
White		ref		
Black		1.0	0.73-1.4	.90
Other		0.91	0.65-1.3	.59
Infection before lung transplant	426	0.90	0.68-1.2	.45
Age (y)	489	1.0	1.0-1.1	.056
Transplant year	489	0.98	0.96-1.0	.097
Creatinine (mg/dL)	422	1.0	0.96-1.1	.30
Body mass index	474	1.0	0.99-1.1	.22
Ischemic time (h)	461	1.0	0.95-1.1	.43
Forced expiratory volume in 1 s (% predicted)	424	1.0	0.99-1.0	.87
Forced vital capacity (% predicted)	427	1.0	1.0-1.0	.27
6-Minute walk test (100 ft)	52	1.0	0.94-1.1	.58
Lung allocation score	208	0.99	0.97-1.0	.31

ref, Reference category.

antigen-presenting cells to secondary lymphoid tissue (thoracic regional lymph nodes and spleen)²⁰ or direct stimulation by dendritic cells in the graft.²¹ T cell receptors recognize the allogeneic HLAs on the donor cells via a

FIGURE 1. Kaplan-Meier survival functions of time to death for adults with cystic fibrosis according to human leukocyte antigen (HLA) mismatch ≥ 3 versus 0 to 2 (n = 2687). Log-rank test: χ^2 (df = 1): 3.9; P = .050. CI, Confidence interval.

FIGURE 2. Kaplan-Meier survival functions of time to death for children with cystic fibrosis according to human leukocyte antigen (HLA) mismatch ≥ 3 versus 0 to 2 ($n = 363$), Log-rank test: χ^2 ($df = 1$): 5.8; $P = .016$. CI, Confidence interval.

direct pathway and peptide fragments of allogeneic HLA presented by recipient HLA molecules through an indirect pathway.²⁰ The HLA class 1 genes are expressed on all nucleated cells, whereas HLA class 2 genes are expressed

primarily on B and T cells, dendritic cells, monocytes, and other antigen-presenting cells.^{22,23}

After LTx, recipients can develop a humoral response to the graft through antibody production against the donor HLAs. These antibodies bind to the allo-HLAs and activate the complement cascade with subsequent complement deposition, endothelial cell injury, and inflammatory injury.²⁴ Antibody-mediated rejection (AMR) is increasing being recognized in LTx on a continuum that also includes latent, silent, and subclinical types, with concomitant circulating donor-specific anti-HLA antibodies (DSAs) and graft C4d deposition being a part of the diagnosis.²⁴ LTx recipients can develop de novo DSAs and non-DSAs that are associated with AMR and can increase the incidence of both BOS and death.²⁴⁻²⁷ In a recent, single-center study of 44 LTx recipients, Lobo and colleagues²⁸ reported that non-DSAs were detected more in their DSA group than the non-DSA group ($P = .0006$), whereas AMR occurred more frequently in the non-DSA group compared with the group without non-DSAs (50% [11 out of 22] vs 0% (0 out of 22); $P = .002$). Of these 44 adult patients (age range, 17-67 years), 30 had CF with a significantly higher proportion being in the DSA group (12 out of 13).²⁸ Thus, these investigators suggested that adult patients with CF may be at higher risk of DSA production and possibly AMR development after LTx.

TABLE 5. Multivariate Cox survival analysis of adults with cystic fibrosis

Variable	Model 1 ($n = 2073$)			Model 2 ($n = 1177$)		
	HR	95% CI	P value	HR	95% CI	P value
Human leukocyte antigen mismatch	1.0	0.95-1.1	.68	1.1	0.97-1.2	.19
Male recipient	1.1	0.92-1.2	.43	1.2	0.96-1.5	.11
Male donor	0.94	0.81-1.1	.37	0.88	0.70-1.1	.27
Race of recipient						
White	ref			ref		
Black	0.91	0.51-1.6	.74	1.2	0.54-2.7	.64
Other	0.72	0.46-1.1	.15	1.2	0.65-2.1	.60
Race of donor						
White	ref			ref		
Black	1.2	1.0-1.5	.029	1.4	1.0-1.8	.030
Other	1.1	0.94-1.4	.19	1.1	0.84-1.5	.47
Infection before lung transplant	1.1	0.99-1.3	.071	1.0	0.84-1.3	.67
Age (y)	0.98	0.97-0.98	<.001	0.97	0.96-0.98	<.001
Transplant year	0.99	0.98-1.0	.15	0.99	0.93-1.0	.69
Creatinine (mg/dL)	1.1	0.93-1.2	.39	1.1	0.95-1.3	.19
Body mass index	1.0	0.98-1.0	.58	1.0	0.96-1.0	.96
Ischemic time (h)	0.97	0.93-1.0	.15	0.99	0.93-1.1	.84
Forced expiratory volume in 1 s (% predicted)	0.99	0.98-1.0	.027	0.99	0.98-1.0	.12
Forced vital capacity (% predicted)	1.0	1.0-1.0	.27	1.00	0.99-1.0	.69
Lung allocation score				1.0	1.0-1.0	.18

HR, Hazard ratio; CI, confidence interval; ref, reference category.

TABLE 6. Multivariate Cox survival analysis of children with cystic fibrosis

Variable	Model 1 (n = 257)			Model 2 (n = 116)		
	HR	95% CI	P value	HR	95% CI	P value
Human leukocyte antigen mismatch	0.87	0.73-1.0	.093	0.71	0.54-0.93	.015
Male recipient	1.1	0.73-1.6	.75	1.3	0.64-2.8	.44
Male donor	0.75	0.53-1.1	.11	1.2	0.59-2.5	.61
Race of recipient						
White	ref			ref		
Black	3.3	1.1-9.9	.035	2.4	0.29-20	.41
Other	1.2	0.61-2.5	.55	0.71	0.27-1.9	.50
Race of donor						
White	ref			ref		
Black	0.98	0.58-1.7	.93	0.74	0.29-1.8	.52
Other	0.44	0.25-0.77	.005	0.41	0.16-1.0	.057
Infection before transplant	0.94	0.65-1.4	.77	1.6	0.82-3.0	.18
Age (y)	1.1	1.0-1.2	.011	0.94	0.82-1.1	.42
Transplant year	1.0	0.96-1.0	.99	1.1	0.87-1.3	.59
Creatinine (mg/dL)	1.1	0.91-1.4	.27	1.2	0.24-6.6	.79
Body mass index	0.98	0.92-1.0	.43	1.1	0.94-1.3	.25
Ischemic time (h)	1.0	0.92-1.2	.59	1.0	0.85-1.3	.75
Forced expiratory volume in 1 s (% predicted)	1.0	0.98-1.0	.87	0.97	0.94-1.0	.15
Forced vital capacity (% predicted)	1.0	0.98-1.0	.94	1.0	0.99-1.1	.11
Lung allocation score				1.0	0.98-1.0	.85

HR, Hazard ratio; CI, confidence interval; ref, reference category.

Increased HLA mismatching being protective and reducing the mortality HR in children with CF after LTx is counterintuitive to current practice. The data regarding humoral immunity in children after LTx are even more limited than what exists in the adult population. Nevertheless, HLA disparities between adult and pediatric recipients as seen in our analysis is consistent with the evolving medical literature in hematopoietic stem cell transplantation.²⁹⁻³¹ With a retrospective study, we cannot determine causality or mechanisms involved, so future research is needed to explore the differences in humoral immunity in adult and pediatric patients with CF.

Several investigators have identified that B lymphocytes transcribe the *CFTR* gene and exhibit CF-defective cAMP-regulated chloride current.³²⁻⁴⁵ With *CFTR* dysfunction being the defect in CF, an alteration in B lymphocyte function may exist in CF, particularly earlier in the disease course when younger patients have more naïve B cells. In support of this theory, patients with CF are known to be poor serologic responders to various vaccines,⁴⁶⁻⁴⁸ suggesting potential B cell dysfunction. Moreover, *Pseudomonas aeruginosa* stimulates B lymphocyte proliferation.^{49,50} Therefore, this pathogen commonly seen in CF may also be playing a role in this immunologic process. Another potential factor is permissive HLA mismatching, which is an evolving concept in allogeneic hematopoietic cell transplantation

where 8 of 8 HLA allele-level matches (HLA-A, -B, -C, and -DRB1) are preferred. Permissive HLA mismatch allows transplantation of single locus mismatches where the locus may not be clinically relevant.^{51,52} Therefore, certain HLA mismatches may not necessarily be significant at a younger age, further suggesting differences in immune response based on age and, potentially, a higher prevalence of immune tolerance in younger LTx recipients versus older patients. Evidence supporting this theory of a more tolerant immune system in children is slowly expanding in the medical literature.⁵³⁻⁵⁶

Our study is limited by the retrospective collection of data from a large database that could potentially not include confounding variables with further potential risk for data entry errors and missing data points. Despite its limitations, our study draws results from a large, multiinstitutional registry database of transplant recipients and thus reduces potential biases observed in single-institution observational studies.

CONCLUSIONS

We found that greater HLA mismatching reduced the risk for death among children with CF who underwent LTx, while there was no impact on survival among adults with CF. With these observed differences in HLA matching between adult and pediatric patients with CF, further research is needed to define humoral immunity in this LTx population in which age-related disparities exists.

TABLE 7. Multivariate Cox survival analysis of children and adults with cystic fibrosis, interacting human leukocyte antigen (HLA) mismatch with age at lung transplantation

Variable	Model 3 (n = 3050)			Model 4 (n = 2330)		
	HR	95% CI	P value	HR	95% CI	P value
HLA mismatch	0.87	0.77-0.99	.030	0.85	0.73-0.99	.044
Age (y/10)	0.63	0.50-0.80	<.001	0.60	0.44-0.80	<.001
Age × HLA mismatch	1.1	1.0-1.1	.023	1.1	1.0-1.1	.038
Male recipient				1.0	0.91-1.2	.59
Male donor				0.93	0.82-1.1	.29
Race of recipient						
White				ref		
Black				1.0	0.61-1.7	.97
Other				0.77	0.53-1.1	.16
Race of donor						
White				ref		
Black				1.2	1.0-1.4	.040
Other				1.0	0.87-1.2	.71
Infection before lung transplant				1.1	0.97-1.2	.14
Transplant year				0.99	0.98-1.0	.35
Creatinine (mg/dL)				1.1	0.96-1.2	.22
Body mass index				1.0	0.99-1.0	.44
Ischemic time (h)				0.98	0.94-1.0	.20
Forced expiratory volume in 1 s (% predicted)				0.99	0.99-1.0	.043
Forced vital capacity (% predicted)				1.0	0.98-1.0	.24

HR, Hazard ratio; CI, confidence interval; HLA, human leukocyte antigen; ref, reference category.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The authors thank Dmitry Tumin for providing statistical expertise in the data analysis.

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Key Words: cystic fibrosis, human leukocyte antigen mismatch, lung transplantation, survival

TABLE E1. Number of patients at risk, by human leukocyte antigen (HLA) mismatch level and year since transplant among a cohort of adults with cystic fibrosis who received a lung transplant

Year since transplant	Patients at risk	
	HLA 0-2	HLA ≥ 3
0	91	2581
1	74	1978
2	66	1591
3	55	1276
4	49	1035
5	35	852
6	30	693
7	26	578
8	20	466
9	17	383
10	14	309

HLA, Human leukocyte antigen.

TABLE E2. Number of patients at risk, by human leukocyte antigen (HLA) mismatch level and year since transplant among a cohort of children with cystic fibrosis who received a lung transplant

Year since transplant	Patients at risk	
	HLA 0-2	HLA ≥ 3
0	0	21
1	1	14
2	2	7
3	3	4
4	4	2
5	5	1
6	6	1
7	7	1
8	8	1
9	9	1
10	10	1

HLA, Human leukocyte antigen.