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Analysis of the Influence of HLA-A Matching Relative to HLA-B and -DR Matching on Heart Transplant Outcomes

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Background. There are conflicting reports on the effect of donor-recipient HLA matching on outcomes in heart transplantation. The objective of this study was to investigate the effects of HLA-A matching relative to HLA-B and -DR matching on long-term survival in heart transplantation. **Methods.** A total of 25 583 patients transplanted between 1988 and 2011 were identified from the International Society for Heart and Lung Transplantation registry. Transplants were divided into 2 donor-recipient matching groups: HLA-A–compatible (no HLA-A mismatches) and HLA-A–incompatible (1-2 HLA-A mismatches). Primary outcome was all-cause mortality. Secondary outcomes were graft failure-, cardiovascular-, infection-, or malignancy-related deaths. **Results.** The risk of all-cause mortality 15 years after transplantation was higher for HLA-A–compatible (vs HLA-A–incompatible) grafts in patients who had HLA-B–, HLA-DR–, or HLA-B,DR–incompatible grafts ($P = 0.027$, $P = 0.007$, and $P = 0.002$, respectively) but not in HLA-B– and/or HLA-DR–compatible grafts. This was confirmed in multivariable Cox regression analysis where HLA-A compatibility (vs HLA-A incompatibility) was associated with higher mortality in transplants incompatible for HLA-DR or HLA-B and -DR (hazard ratio [HR], 1.59; 95% confidence interval [95% CI], 1.11-2.28; $P = 0.012$ and HR, 1.69; 95% CI, 1.17-2.43; $P = 0.005$, respectively). In multivariable analysis, the largest compromise in survival for HLA-A compatibility (vs HLA-incompatibility) was for chronic rejection in HLA-B– and -DR–incompatible grafts (HR, 1.91; 95% CI, 1.22-3.01; $P = 0.005$). **Conclusions.** Decreased long-term survival in heart transplantation was associated with HLA-A compatibility in HLA-B,DR–incompatible grafts.

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The most common cause of death after heart transplantation is cardiovascular events and graft failure.[1] Today, donor hearts are not selected on the basis of HLA matching, and HLA typing is mainly applied to determination of donor-specific antibodies in sensitized heart transplant recipients. ABO blood group compatibility, size of recipient and donor, age, sex, and medical urgency are the main criteria for matching potential recipients with the appropriate donor.[2]

In the field of kidney transplantation, there is strong support for the beneficial effect of minimizing donor-recipient HLA incompatibility on improvement of the long-term prognosis of kidney transplant patients.[3] Generally, an impact on cardiac transplant survival for HLA matching has been controversial.[4-9] Opelz and Wujciak[8] showed that 3-year rate of heart graft survival correlated with HLA compatibility. Based on meta-analysis of the available evidence, we have previously shown a significant association between fewer HLA-DR mismatches and reduced incidence of acute rejection and increased graft survival.[10] Others have found no association between the HLA loci, combined or separately, and outcome.[11-13]

Bucin et al[14] previously showed a favorable effect of HLA-A–incompatible grafts on long-term renal graft survival in cyclosporine (CYA)-treated recipients of HLA-B,DR–incompatible transplants. It was hypothesized that incompatibility between

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donor and recipient for HLA-A–related antigens induces a downregulatory reaction on the immune response to incompatible HLA-B and HLA-DR antigens.[15] This prompts the question whether similar observation can be made in heart transplantation, that is, an interaction between HLA-A matching and the other HLA loci, which impact long-term survival. The aim of this study was to investigate possible associations between HLA-A matching in relation to HLA-B, -DR matching and long-term survival after heart transplantation.

MATERIALS AND METHODS

Source Of Data

The International Society for Heart and Lung Transplantation (ISHLT) International Registry for Heart and Lung Transplantation (www.ishlt.org) includes data since 1980s and contains almost 400 variables, including pretransplantation, transplantation, discharge, and follow-up variables. Posttransplant information is reported at the end of the annual follow-up period and at the time of death. The date of death after heart transplantation is provided by the transplant center. A complete list of data collectives, participating institutions, and ISHLT registration data elements are available at http://www.ishlt.org/registries/.

Patients And Study Design

Data from heart donors and the corresponding recipients transplanted between January 1, 1988, and June 31, 2011, were collected from the ISHLT registry (n = 93 507). Pediatric cases (recipients younger than 18 years, n = 13 136); recipients with panel-reactive antibodies (PRA) of 10% or greater (class I or class II) (n = 4 483), history of previous cardiac surgery including mechanical circulatory support, or previous transplantation (n = 10 129); recipients who died intraoperatively (n = 726); and those with missing value on recipient or donor HLA-A, duration of follow-up, or cause of death not reported (n = 39 450) were excluded. The final study population comprised 25 583 patients with at least 1 day of follow-up duration. The latest annual follow-up was on October 9, 2011. The primary endpoint was all-cause mortality. Secondary endpoints were mortality attributable to graft failure (primary failure, rejection: hyperacute, acute or chronic, technical, graft infection, recurrent disease, nonspecific), cardiovascular causes (myocardial infarction, cardiac arrest, arterial embolism, ventricular failure, coronary artery disease, atherosclerosis, rhythm disorder, carditis, aortic aneurysm, cardiogenic shock, other), infection (bacterial septicemia, bacterial pneumonia, bacterial—other, viral cytomegalovirus, hepatitis, viral septicemia, viral—other, fungal, protozoal, mixed), or malignancy (metastatic, primary, posttransplant lymphoproliferative disorder, lymphoma, skin, other) as defined by the ISHLT Registry. The Ethics Committee for Clinical Research at Lund University, Sweden approved the study protocol.

Statistical Analysis

Statistical analyses were performed using the Stata MP statistical package version 13.1 (2013) (StataCorp LP, College Station, TX). Unpaired Mann-Whitney *U* tests or *t* tests were used to compare continuous variables, and χ^2 or Fisher exact tests were used to compare categorical variables among groups. Log-rank test was used to compare the Kaplan-Meier survival curves. Independent predictors of cumulative mortality were identified using Cox proportional hazard (CPH) regression. Any variable from the univariable test (simple CPH) with a *P* value less than 0.25 was selected as a candidate for stepwise backward selection Cox regression analysis, resulting in a main effect model. We further split episodes into 2 episodes at implied time points. Each resulting covariate record contained the follow-up on 1 subject through 1 time band.[16] Hazard ratios (HRs) are presented with 95% confidence intervals (95% CIs). All tests were 2-sided, and *P* values less than 0.05 were deemed significant.

To minimize potential bias arising from missing data, multiple imputation was performed using the chained equations imputation technique as described by White et al.[17] The imputation method was predictive mean matching for continuous variables, logistic regression for binary variables, and ordered logistic for ordinal variables. The number of iterations for each chain was 10, and the number of imputed data sets was 10.

RESULTS

In total, the 25 583 patients accrued 157 938 patient-years of observation. Median follow-up time was 6.0 (range, 0-23.6) years. The mean recipient and donor age was 51 ± 11 and 33 ± 12 years, respectively, and 20% of the recipients and 31% of the donors were women. The most common diagnoses were nonischemic cardiomyopathy (48%) and ischemic cardiomyopathy (45%). The overall patient survival rates were 56% after 10 years and 25% after 20 years. A total of 10 233 patients (40%) died during follow-up. The main causes of death were major adverse cardiovascular event (n = 2 337), graft failure (n = 1 762), malignancy (n = 1 710), and infection (n = 1 598).

The study population was divided into 2 groups; patients with HLA-A–compatible (no HLA-A mismatches) and HLA-A–incompatible (1-2 HLA-A mismatches) grafts. As shown in Table 1, there were significant differences between the groups in diagnosis, use of amiodarone, use of inotropic support, and medical condition at transplant. The median recipient age was slightly higher in the HLA-A–incompatible group (54 vs 53 years; $P = 0.048$). The proportion of patients with donor-recipient sex match was higher in the HLA-A–compatible group (74.7% vs 70.9%; $P = 0.003$). Other demographic data, blood group, blood group match, previous blood transfusion, comorbidity, hemodynamic, and laboratory status were similar in the 2 groups.

Tacrolimus (TAC), mycophenolate mofetil (MMF), and steroids as maintenance therapy at discharge were significantly more common among patients with HLA-A–incompatible grafts (28.4% vs 23.5%, $P = 0.005$; 64.0% vs 50.6%, $P < 0.001$; and 83.6% vs 62.8%, $P < 0.001$, respectively). The CYA and azathioprine were more common in the HLA-A–compatible group (78.0% vs 73.6%, $P = 0.006$ and 57.1% vs 52.0%, $P = 0.004$, respectively). Induction basiliximab was more common in the HLA-A–incompatible group (8.2% vs 4.6%; $P = 0.001$) whereas induction steroids were more common in the HLA-A–compatible group (84.7% vs 79.2%; $P < 0.001$). As seen in Table 2, in the immunotherapy decrease during the follow-up and at 15 years after transplantation, there were no differences between the groups. At 1 year after transplantation, a greater proportion of patients in the HLA-A–incompatible group received

TABLE 1.

Characteristics of patients with HLA-A–Compatible and HLA-A–Incompatible grafts

Variables	N	HLA-A–compatible (n = 1 304)	HLA-A–incompatible (n = 24 279)	*P*
Recipient				
Age, y	25 572	53 (44-59)	54 (46-60)	0.048
Female sex, %	25 582	250 (19.2)	4961 (20.4)	0.270
Weight, kg	21 379	77.0 ± 15.4	77.9 ± 15.8	0.083
Height, cm	21 193	173.9 ± 9.1	173.9 ± 9.5	0.924
Diagnosis	25 529			0.033
Coronary artery disease		569 (43.9)	10 896 (45.0)	
Cardiomyopathy		614 (47.4)	11 682 (48.2)	
Miscellaneous		47 (3.6)	605 (2.5)	
Congenital		32 (2.5)	419 (1.7)	
Heart valve disease		34 (2.6)	631 (2.6)	
Blood group	25 516			0.088
A		614 (47.2)	10 860 (44.9)	
AB		74 (5.7)	1356 (5.6)	
B		143 (11.0)	3222 (13.3)	
O		470 (36.0)	8777 (36.3)	
Amiodarone	12 469	120 (30.8)	3076 (25.5)	0.018
Inotrop support prior to transpl	19 819	236 (35.0)	8151 (42.6)	<0.001
Obstructive pulmonary disease	12 589	13 (3.4)	383 (3.1)	0.799
Diabetes (insulin-treated)	12 803	66 (17.9)	2387 (19.2)	0.545
Hypertension	12 683	150 (38.7)	4700 (38.2)	0.863
Preoperative cytomegalovirus	7 380	181 (74.2)	5162 (72.3)	0.527
Dialysis pretransplant	12 427	6 (1.6)	318 (2.6)	0.216
Medical condition at transplant	20 041			0.030
Home		372 (52.2)	9170 (47.4)	
Hospital		87 (12.2)	2360 (12.2)	
Intensive care unit		254 (35.6)	7798 (40.4)	
Ventilator	19 326	16 (2.6)	403 (2.2)	0.498
ECMO	19 330	1 (0.2)	45 (0.2)	0.683
Creatinine most recent, μmol/L	13 836	106 (88-134)	106 (88-133)	0.649
PVR (wood units)	11 035	2.1 (1.5-3.0)	2.2 (1.4-3.2)	0.676
Previous blood transfusion	8 214	100 (37.3)	3224 (40.6)	0.285
Albumin, g/L	6 262	38.0 ± 6.5	37.1 ± 7.5	0.147
Stroke	12 346	1 (0.3)	147 (1.2)	0.191
Working for income	3 860	8 (8.5)	236 (6.3)	0.386
Donor				
Age, y	25 573	32 (22-43)	31 (22-43)	0.476
Female sex	25 565	400 (30.7)	7602 (31.3)	0.644
Weight, kg	23 599	76.3 ± 16.7	77.4 ± 16.8	0.024
Height, cm	21 112	175.5 ± 9.0	174.9 ± 9.3	0.032
Blood group	25 519			0.122
A		537 (41.3)	9 488 (39.2)	
AB		37 (2.8)	651 (2.7)	
B		114 (8.8)	2585 (10.7)	
O		613 (47.1)	11 494 (47.5)	
Diabetes	13 942	4 (0.9)	271 (2.0)	0.103
Cytomegalovirus (positive)	20 979	447 (55.2)	11 791 (58.5)	0.064
Hepatitis C virus (positive)	13 696	3 (0.8)	141 (1.1)	0.801
Hypertension	14 038	46 (10.2)	1698 (12.5)	0.141
Ischemic time, min	21 104	174 (126-215)	170 (127-212)	0.372
Transplant era				
1988-2000	25 583	824 (63.2)	15 255 (62.8)	0.794
2001-2011	25 583	480 (36.8)	9024 (37.2)	0.794
Blood group match	25 481	1119 (86.1)	20 874 (86.3)	0.856
Sex match	25 564	972 (74.7)	17 196 (70.9)	0.003

Qualitative data are expressed as n (%), and quantitative data as mean ±SD or median (interquartile range) as appropriate.

HLA-A–compatible, grafts with no HLA-A mismatches; HLA-A–incompatible, graft with 1-2 HLA-A mismatches; N, number of non-missing values. PVR, pulmonary vascular resistance; ECMO, extracorporeal membrane oxygenation; transpl, transplant.

TABLE 2.

Immunotherapy at follow-up

	1 y			5 y		
	HLA-A comp	**HLA-A incomp**	***P***	**HLA-A comp**	**HLA-A incomp**	***P***
CYA	244 (38.6)	4743 (28.8)	<0.001	218 (39.9)	4874 (38.9)	0.652
TAC	165 (30.0)	4477 (32.0)	0.312	125 (25.6)	3410 (28.8)	0.130
MMF	285 (56.7)	7010 (57.3)	0.791	228 (53.0)	5545 (51.4)	0.516
AZA	78 (12.3)	1168 (7.1)	<0.001	69 (12.6)	1676 (13.4)	0.653
RAP	24 (4.8)	648 (5.3)	0.603	30 (7.0)	906 (8.4)	0.292
CS	336 (53.1)	7116 (43.3)	<0.001	197 (36.0)	4868 (38.8)	0.184
		10 y			15 y	
	HLA-A comp	HLA-A incomp	*P*	HLA-A comp	HLA-A incomp	*P*
CYA	134 (62.3)	2 989 (67.8)	0.097	63 (81.8)	825 (78.3)	0.465
TAC	30 (14.0)	715 (16.2)	0.380	10 (13.0)	150 (14.2)	0.762
MMF	68 (31.6)	1609 (36.5)	0.149	21 (27.3)	344 (32.6)	0.331
AZA	58 (27.0)	1494 (33.9)	0.037	32 (41.6)	412 (39.1)	0.668
RAP	9 (4.2)	293 (6.6)	0.155	4 (5.2)	121 (11.5)	0.129
CS	96 (44.7)	2349 (53.2)	0.014	53 (68.8)	614 (58.3)	0.069

Values in parenthesis are percentages.

AZA, azathioprine; RAP, rapamycin; CS, corticosteroids.

steroids for rejection (20.6% vs 15.3%, P <0.001). However, at 5, 10 and 15 years after transplantation, there was no difference between the groups in the proportion of patients receiving steroids for rejection (P = 0.114, P = 1.000, and P = 1.000, respectively).

We first examined the effect of HLA-A compatibility versus HLA-A incompatibility for the entire cohort on all-cause mortality (Figure 1). We found no significant difference in survival between the groups over the entire follow-up period (P = 0.187, Log-rank test). However, as shown in Figure 1, there was a trend toward lower survival with HLA compatibility (vs HLA incompatibility; P = 0.064, Log rank test) during the later time interval (>15 years after transplantation).

To determine whether the other HLA loci interacted with HLA-A, we performed a subgroup analysis including only HLA-B–, HLA-DR– or HLA-B–, and DR–incompatible/compatible grafts. In the later time interval (>15 years), HLA-A compatibility was associated with lower survival in transplants incompatible for HLA-B (P = 0.027, Log-rank test), and the decrease in survival became more pronounced in HLA-DR–incompatible grafts (P = 0.007, Log-rank test) and even more so in HLA-B– and -DR–incompatible grafts (P = 0.002, Log-rank test) (Figures 2A, C, and E). This observation was not found in compatible HLA-B, -DR or -B,-DR grafts (Figures 2B, D, and F).

We next performed a multivariable Cox regression analysis resulting in a final main model that incorporated 18 significant independent covariates. When HLA-A compatibility and interactions between HLA-A and HLA-B, HLA-DR, or HLA-B,DR were added to the model, we found no significant difference in mortality between the groups in the early time period after transplantation. Nor was there any significant difference in the late era for the entire cohort (P = 0.102). However, among those who survived to 15 years after transplantation, an increased mortality was perceived for HLA-A compatibility versus HLA-A incompatibility in HLA-DR–incompatible grafts (HR, 1.59; 95% CI, 1.11-2.28; P = 0.012, CPH test) and in HLA-B,DR–incompatible grafts (HR, 1.69; 95% CI, 1.17-2.43; P = 0.005, CPH test) (Table 3A). Stratification of recipients by number of HLA-A mismatches further reinforced these results, demonstrating an association between fewer mismatches and higher mortality starting 15 years after transplantation. Figure 3 shows this trend in HLA-B,DR–incompatible grafts. These results were reflected in the adjusted HRs for HLA-A compatibility grafts (0 HLA-A mismatch) versus 2 HLA-A mismatches (HR, 1.79; 95% CI, 1.22-2.61; P = 0.003) and 1 HLA-A mismatch (HR, 1.68; 95% CI, 1.14-2.47; P = 0.008), respectively.

We performed the same univariate and multivariable analyzes for the secondary endpoints, that is, cause of death. There was a trend for lower survival in the later posttransplant eras for HLA compatibility for cardiovascular-, infection-, and malignancy-related deaths but not for graft failure-related deaths. As cardiovascular disease could be a manifestation of chronic rejection and infection and malignancy related

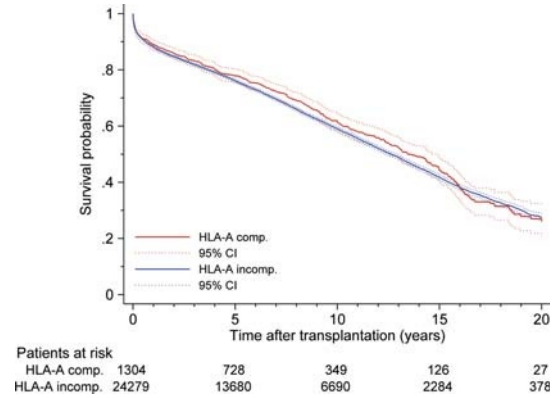

FIGURE 1. Kaplan-Meier survival curves according to HLA-A–compatible grafts versus HLA-A–incompatible grafts in all patients for all-cause mortality (P = 0.187, Log-rank test). The red solid line shows the observed cumulative survival and red dotted lines show the 95% confidence interval (estimated with Kaplan- Meier survival function) in the HLA-A–compatible cohort. The blue solid line shows survival, and the blue dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) for transplanted patients in the HLA-A–incompatible cohort.

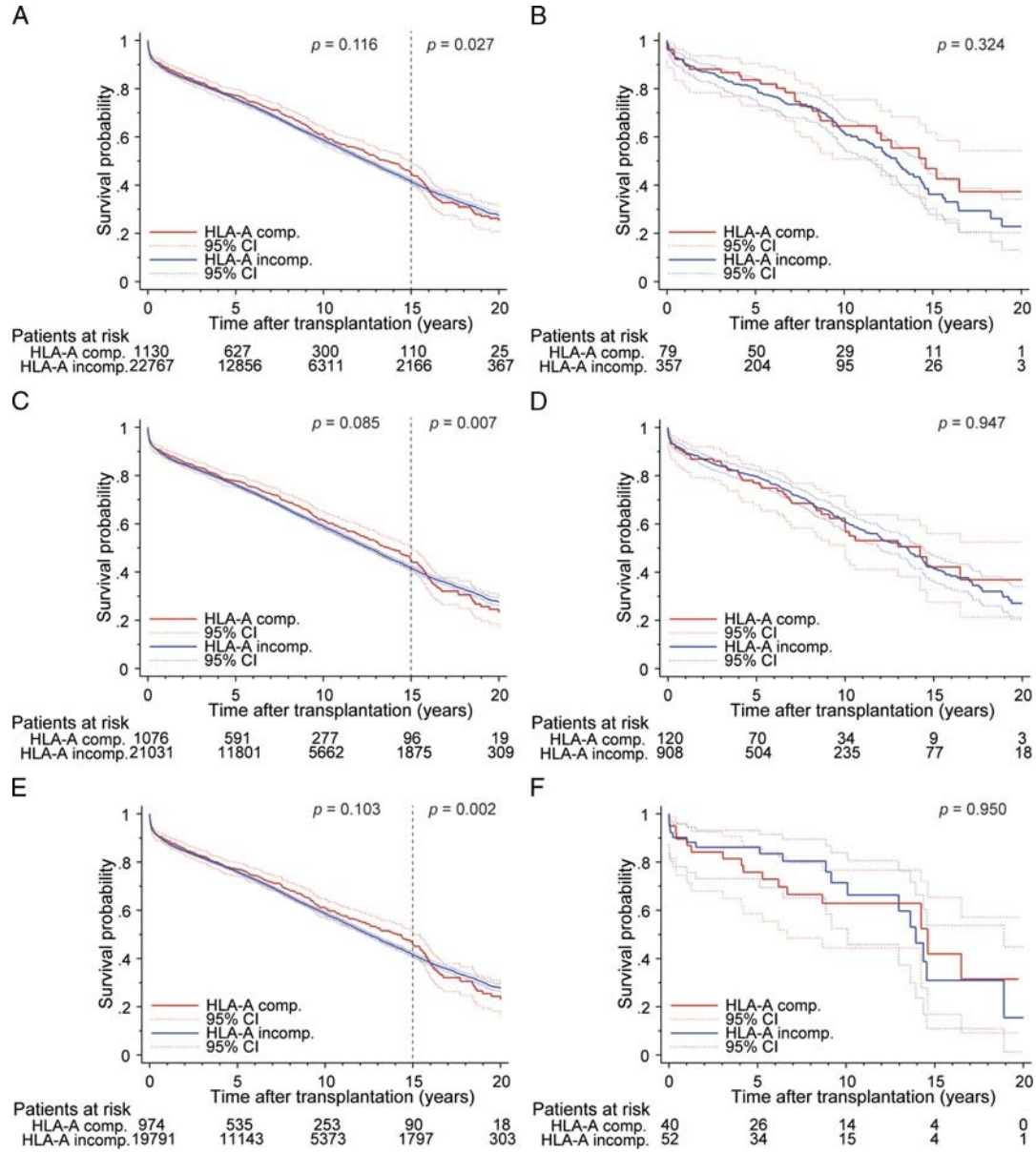

FIGURE 2. Kaplan-Meier survival curves according to HLA-A compatible grafts versus HLA-A incompatible grafts for all cause-mortality in panel A, HLA-B incompatible transplants, B, HLA-B compatible transplants, C, HLA-DR incompatible transplants, D, HLA-DR compatible transplants, E, HLA-B & DR incompatible transplants and F, HLA-B and DR compatible transplants. The red solid line shows the observed cumulative survival and red dotted lines show the 95% confidence interval (estimated with Kaplan- Meier survival function) in the HLA-A compatible cohort. The blue solid line shows survival and blue dotted lines show the 95% confidence interval (estimated with Kaplan- Meier survival function) for transplanted patients in the HLA-A incompatible cohort. Statistical test: Log-rank test.

to immunosuppressive agents given for chronic rejection, we studied the combined deaths caused by chronic rejection, cardiovascular disease, infection, and malignancy. HLA-compatible grafts had lower survival in the later post-transplant time eras (P = 0.044, Log-rank test). Table 3B shows the results of the multivariable analysis for this outcome. Noteworthy, HR increased from 1.69 to 1.91 (95% CI, 1.22-3.01; P = 0.005) in HLA-B,DR–incompatible grafts. However, for the entire cohort, the HR was not significant (P = 0.063). Thus, in multivariable analysis, the largest compromise in survival for HLA-A compatibility (vs HLA incompatibility) was for chronic rejection (including cardiovascular-, infection- and malignancy-related deaths) in HLA-B– and -DR–incompatible grafts, which is also shown in Figure 4.

We also analyzed HLA-B match versus mismatch and HLA-DR match versus mismatch in different HLA combinations (Tables 4A and 4B). Although a trend toward lower survival seen in the survival curves for HLA-B compatibility versus HLA-B incompatibility in later posttransplant eras, this could not be confirmed in univariate or multivariable analyses.

Finally we examined the effects of HLA-A matching on graft loss, defined as death or repeat transplantation (n = 575). The results remained essentially unchanged.

DISCUSSION

This represents the first report to specifically investigate the association between HLA-A donor-recipient matching

TABLE 3A.

Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y posttransplant) affecting All-Cause mortality for HLA-A compatibility versus incompatibility in different HLA combinations

			Univariable		Multivariable	
		N	Hazard ratio	*P*	Hazard ratio	*P*
HLA-A						
Incomp		24 279	1.00		1.00	
Comp		1 304	1.36 (0.98-1.90)	0.066	1.32 (0.95-1.84)	0.102
HLA-A	HLA-B					
Incomp	Incomp	22 767	1.00		1.00	
Comp	Incomp	1 130	1.46 (1.04-2.05)	0.028	1.41 (1.00-1.98)	0.052
HLA-A	HLA-DR					
Incomp	Incomp	21 031	1.00		1.00	
Comp	Incomp	1 076	1.64 (1.14-2.36)	0.007	1.59 (1.11-2.28)	0.012
HLA-A	HLA-B and -DR					
Incomp	Incomp	19 791	1.00		1.00	
Comp	Incomp	974	1.75 (1.22-2.51)	0.002	1.69 (1.17-2.43)	0.005

Values in parenthesis are 95% confidence intervals. Incomp, incompatible; Comp, compatible. n, number of patients. Adjusted for transplant era, donor age (year), recipient work for income, recipient diabetes, recipient age (year), albumin level (g/L), donor hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transfusion, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy; mycophenolate mofetil, maintenance therapy; corticosteroids, maintenance therapy; azathioprine, induction therapy; OKT3, Orthoclone OKT3.

in relation to other HLA loci using the ISHLT database in adult heart transplant patients. We found an association between increased mortality in the late posttransplant period and higher degree of HLA-A matching in patients with HLA-B– and/or -DR–incompatible grafts. Early reports found that well-matched heart transplants had a significantly

TABLE 3B.

Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting mortality caused by chronic rejection, cardiovascular disease, infection or malignancy for HLA-A compatibility versus incompatibility in different HLA combinations

			Univariable		Multivariable	
		N	Hazard Ratio	*P*	Hazard Ratio	*P*
HLA-A						
Incomp		24 279	1.00		1.00	
Comp		1304	1.52 (1.01-2.28)	0.046	1.48 (0.98-2.23)	0.063
HLA-A	HLA-B					
Incomp	Incomp	22 767	1.00		1.00	
Comp	Incomp	1130	1.68 (1.11-2.55)	0.015	1.62 (1.07-2.47)	0.024
HLA-A	HLA-DR					
Incomp	Incomp	21 031	1.00		1.00	
Comp	Incomp	1076	1.82 (1.16-2.84)	0.009	1.76 (1.13-2.77)	0.013
HLA-A	HLA-B and -DR					
Incomp	Incomp	19 791	1.00		1.00	
Comp	Incomp	974	1.98 (1.26-3.10)	0.003	1.91 (1.22-3.01)	0.005

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (y), recipient working for income, recipient age (y), albumin level (g/L), recipient weight (kg), donor hepatitis C virus status, recipient diabetes, recipient previous transfusion, recipient on ventilator, donor sex, recipient stroke, donor cytomegalovirus status, maintenance therapy; corticosteroids, maintenance therapy; cyclosporine, maintenance therapy; mycophenolate mofetil, induction therapy; antithymocyte globulin.

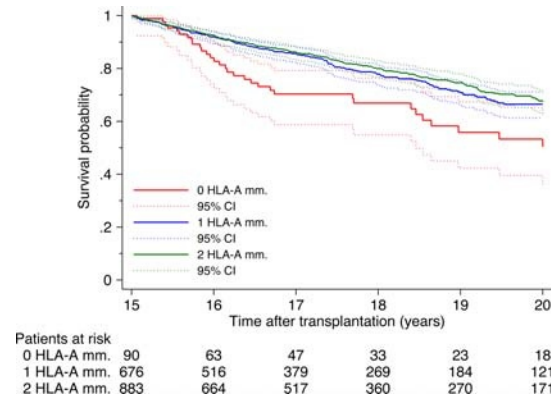

FIGURE 3. Kaplan-Meier survival curves by number of HLA-A mismatches in the 15 to 20 years posttransplant time interval in HLA-B,DR–incompatible grafts for all-cause mortality. The red solid line shows the observed cumulative survival and red dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) in the HLA-A cohort with zero mismatch. The blue solid line shows survival, and the blue dotted lines show the 95% confidence interval (estimated with Kaplan- Meier survival function) for transplanted patients in the HLA-A cohort with 1 mismatch. The green solid line shows survival, and the green dotted lines show the 95% confidence interval (estimated with Kaplan- Meier survival function) for transplanted patients in the HLA-A cohort with 2 mismatches. mm; mismatches.

better graft survival rate than poorly matched ones.[4,8] Although the majority of later studies confirmed this correlation, some studies have indicated that HLA matching does not improve outcomes in heart transplantation.[11,18] No study to date has evaluated the possible association between HLA compatibility and long-term survival, that is, beyond 15 years after transplantation.[1,10] Moreover, analysis of interactions between the different HLA-loci is lacking in the previous studies. The fact that HLA-A mismatching was associated with lower mortality related to chronic rejection indicated a possible immunologic cause for the improved survival. HLA-DR or HLA-B mismatching was not associated

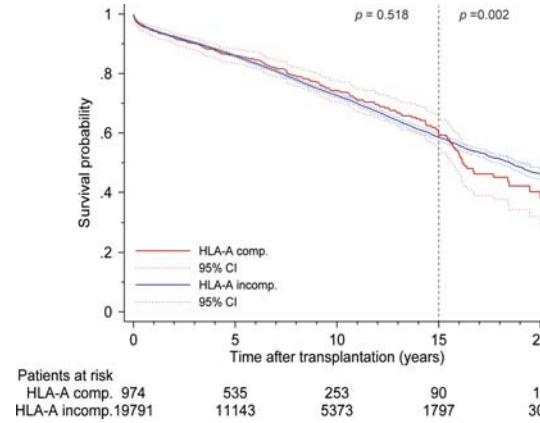

FIGURE 4. Kaplan-Meier survival curves according to HLA-A–compatible grafts versus HLA-A–incompatible grafts in HLA-B– and -DR–incompatible transplants for mortality caused by chronic rejection, cardiovascular disease, infection, or malignancy. The red solid line shows the observed cumulative survival, and the red dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) in the HLA-A–compatible cohort. The blue solid line shows survival, and the blue dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) for transplanted patients in the HLA-A–incompatible cohort. Statistical test: Log-rank test.

TABLE 4A.

Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting All-Cause mortality for HLA-B compatibility versus incompatibility in different HLA combinations

			Univariable		Multivariable	
		N	Hazard ratio	*P*	Hazard ratio	*P*
HLA-B						
Incomp		23 897	1.00		1.00	
Comp		436	1.01 (0.50-2.04)	0.971	0.97 (0.48-1.96)	0.933
HLA-B	HLA-A					
Incomp	Incomp	22 767	1.00		1.00	
Comp	Incomp	357	1.10 (0.49-2.45)	0.824	1.01 (0.45-2.28)	0.981
HLA-B	HLA-DR					
Incomp	Incomp	20 765	1.00		1.00	
Comp	Incomp	301	0.90 (0.33-2.40)	0.828	0.85 (0.32-2.30)	0.753
HLA-B	HLA-A and -DR					
Incomp	Incomp	19 791	1.00		1.00	
Comp	Incomp	276	1.18 (0.44-3.17)	0.739	1.09 (0.40-2.95)	0.864

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (y), recipient work for income, recipient diabetes, recipient age (y), albumin level (g/L), donor hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transfusion, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy; mycophenolate mofetil, maintenance therapy; corticosteroids, maintenance therapy; azathioprine, induction therapy; OKT3.

with improved survival in the whole cohort or in incompatible grafts of the other 2 loci.

We believe that tolerance is a crucial part of the immune response in transplantation and in other responses to, for example, cancer, infection, or autoimmunity. In our opinion, the immune response comprises interactions between upregulative and downregulative processes. As an illustration of a general principle, the activation of upregulative response may induce and activate a downregulative immune response as shown by interaction of CD28 and CTLA-4 antigens with CD80, CD86 ligands.[19,20] In contrast to the 1980s or 1990s at the present time, numerous of tolerance inducing genes/structures have been identified, for example, nonclassical HLA class I genes (HLA-G, -F, -E), where the tolerance induction of HLA-G genes were extensively studied in pregnancy and transplantation.[21,22] Furthermore, some of the epitopes of HLA-A antigens have been found in association with decreased risk of delayed allograft function in renal transplantation.[23] It could be speculated whether our results may be explained by the existence of a gene involved in the induction of tolerance across a class I disparity. Actually, the possibility of such a gene was found likely in swine model,[24] but no gene able to induce tolerance to class I–mismatched grafts has been evaluated in cardiac transplantation in humans to date.

Our results may agree with the proposed interactive effect of the HLA-A class I region and the HLA class II region on the regulation of the immune response. Briefly, the incompatibility between donor and recipient for class I HLA-A–related antigens in association/linkage disequilibrium with HLA-A alloantigens induces a downregulatory reaction on the immune response to incompatible HLA-B and HLA-DR antigens.[15,25] However, in our study, the number of patients at risk 15 years after transplantation was small, which should prompt caution in interpreting the results.

The time from an initiation of transplant rejection to graft failure is years for chronic rejection and days to months for acute rejection. Chronic rejection or cardiac allograft vasculopathy (CAV) is characterized by a progressive fibroproliferative disease, resulting in intimal thickening and occlusion of the grafted coronary vessels.[26] Although some studies have shown a correlation between HLA matching and CAV,[27,28] several studies have failed to show any association between HLA matching and development of CAV.[4,29,30] However, compared with our report, these studies had shorter follow-up time and looked at the incidence of CAV in contrast to mortality due to CAV. Studies have found an increased level of antibodies to cardiac self-antigens, myosin and vimentin, as well as an increased frequency of IL-17 secreting $CD4^+$ T cells against myosin and vimentin,[31] in patients with CAV, indicating that they may be involved the pathogenesis of CAV. Also, donor-specific antibodies to mismatched HLA are significantly associated with the development of antibodies to self-antigens.[31] However, no such data were available for analysis in this study.

Our results may have been influenced by differences in immunotherapy given to the patients in the HLA-A–compatible and –incompatible groups. The TAC and MMF were more common among the HLA-A–incompatible patients at discharge. This could be because the HLA-A–incompatible patients experienced more rejection episodes shortly after transplantation , and consequently CYA and azathioprine were exchanged with the more modern drugs, TAC and MMF. Furthermore, a higher proportion of the patients in the HLA-A–incompatible group were treated with steroids for rejection at 1 year. This may have lead to higher incidence of chronic rejection in the long run. We aimed to correct for the differences in immunotherapy by performing a multivariable analysis.

TABLE 4B.

Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting All-Cause mortality for HLA-DR compatibility versus incompatibility in different HLA combinations

			Univariable		Multivariable	
		N	Hazard ratio	*P*	Hazard ratio	*P*
HLA-DR						
Incomp		22 107	1.00		1.00	
Comp		1028	0.91 (0.57-1.44)	0.684	0.91 (0.58-1.45)	0.702
HLA-DR	HLA-A					
Incomp	Incomp	21 031	1.00		1.00	
Comp	Incomp	908	1.02 (0.64-1.64)	0.931	1.02 (0.64-1.65)	0.923
HLA-DR	HLA-B					
Incomp	Incomp	20 765	1.00		1.00	
Comp	Incomp	875	0.87 (0.52-1.45)	0.586	0.88 (0.53-1.48)	0.638
HLA-DR	HLA-A and -B					
Incomp	Incomp	19 791	1.00		1.00	
Comp	Incomp	805	0.96 (0.57-1.61)	0.888	0.98 (0.58-1.65)	0.944

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (y), recipient work for income, recipient diabetes, recipient age (y), albumin level (g/L), donor hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transfusion, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy; mycophenolate mofetil, maintenance therapy; corticosteroids, maintenance therapy; azathioprine, induction therapy; OKT3.

The results of this study carry limitations associated with the retrospective analysis of a registry database. We do not know to what degree the donors in the individual transplant centers were allocated based on HLA matching. Therefore, the distribution of HLA matching may not represent random chance but influenced by unknown factors, not accounted for. Missing values in this study were accounted for by multiple imputation technique, which is probably the best method available today. Data on donor-specific antibodies were not available in the ISHLT database. To avoid the confounding effect of preexisting donor-specific antibodies, recipients with a history of cardiac surgery, including ventricular assist device or previous transplantation, were excluded. We also excluded patients with PRA of 10% or greater, the cutoff value above which PRA is associated with worse survival after transplantation. Our analysis was limited to the HLA-A, -B, and -DR loci. Unfortunately, the ISHLT registry does not collect data on HLA-DQ and -C typing. In the future, the addition of HLA-C and DQ may improve risk stratification based on HLA matching.

In conclusion, this study represents the largest analysis of HLA-matching in heart transplantation with a follow-up that is longer than any other study on HLA and heart transplantation. Study limitations necessitate caution in the interpretation of the results, but the fact that HLA-A mismatching was associated with lower mortality related to chronic rejection indicated a possible immunologic cause for the improved survival. Elucidating a possible protective mechanism of HLA-A mismatching on patient and graft survival should be the subject of further investigation. This knowledge could help guide diagnostic and therapeutic interventions in patients with HLA-A–compatible and HLA-B,DR–incompatible grafts.

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