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Association of HLA Mismatch With Death With a Functioning Graft After Kidney Transplantation: A Collaborative Transplant Study Report

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HLA mismatches may correlate with risk of death with a functioning graft (DWFG) because of requirement for higher immunosuppression doses and more antirejection therapy. Deceased-donor kidney transplants (n = 177 584) performed 1990–2009 and reported to the Collaborative Transplant Study were analyzed. The incidence of DWFG was found to be 4.8% during year 1 posttransplant and 7.7% during years 2–5 (Kaplan–Meier estimates). Most frequent causes of DWFG were infection, cardiovascular disease and malignancy (32.2%, 30.9% and 3.6% in year 1; 16.4%, 29.6% and 15.9% in years 2–5). HLA-A + B + DR mismatches were significantly associated with DWFG during year 1 ($p < 0.001$), a correlation that diminished but persisted during years 2–5 ($p < 0.001$). HLA mismatch was associated with DWFG because of infection ($p < 0.001$ during year 1, $p = 0.043$ during years 2–5) or cardiovascular disease ($p < 0.001$ during year 1, $p = 0.030$ during years 2–5) but not malignancy. There was also a significant association between HLA mismatch and hospitalization for viral ($p < 0.001$) or bacterial ($p = 0.002$) infection. Multivariable analysis showed that mismatches for HLA class II were more strongly associated with both hospitalization and DWFG than mismatches for HLA class I.

Key words: Cardiovascular disease, death, HLA matching, infection, kidney transplantation

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CTS, Collaborative Transplant Study; DWFG, death with a functioning graft; HR, hazard ratio; MM, mismatch; MPA, mycophenolic acid; OR, odds ratio; PRA, panel reactive antibodies; Ref, reference; SE, standard error; UNOS, United Network for Organ Sharing; USRDS, US Renal Data System

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Introduction

Death with a functioning graft (DWFG) is the most common reason for patient death after kidney transplantation, particularly in older patients or in recipients with risk factors such as diabetes mellitus (1). The most frequent causes of DWFG are cardiovascular disease, infection and malignancy (2–5). A US Renal Data System (USRDS) analysis of 50 246 deceased-donor kidney transplants followed for a median of 3 years posttransplant observed that 5982 out of 7842 deaths (76.3%) occurred in patients with a functioning graft (3).

The type and intensity of immunosuppression following kidney transplantation play an important contributory role in the risk of death unrelated to graft function, particularly the three most common causes of such deaths—cardiovascular disease, infection and malignancy (2). Maintenance immunosuppressive agents, notably calcineurin inhibitors and steroids, increase cardiovascular risk factors such as diabetes mellitus, hyperlipidemia and hypertension (6,7) whereas calcineurin inhibitors and azathioprine have been linked to posttransplant malignancy (8). Use of more potent maintenance immunosuppressive agents can increase the risk of posttransplant infection (9,10) whereas antilymphocyte antibody induction therapy is associated with an increased risk of both infection and malignancy (5,11,12).

The Collaborative Transplant Study (CTS) is a prospective study which collects data on solid organ transplants from more than 400 transplant centers worldwide (www.ctstransplant.org). Based on CTS data from kidney transplant recipients, we have previously shown a highly significant association between the number of recipient–donor HLA mismatches and the need for higher maintenance doses of calcineurin inhibitors, antimetabolite agents and steroids (13) as well as greater requirement for antirejection treatment (14). This prompts the question of whether the number of HLA mismatches correlates with the risk of DWFG after kidney transplantation and, specifically, with death caused by infection, cardiovascular disease or malignancy.

In the current analysis, CTS data from more than 177 000 kidney transplant recipients were examined to investigate

a possible relationship between HLA mismatches and the risk of DWFG overall and because of cardiovascular causes, infection or cancer.

Methods

CTS data were analyzed from 177 584 recipients of a deceased-donor kidney transplant performed between 1990 and 2009 for whom recipient and donor HLA typing data were available. Recipients of multiorgan transplants, including combined kidney–pancreas transplants, were excluded. HLA typing was performed locally at the tissue typing laboratories of participating centers, and analyzed according to broad HLA specificities. A subanalysis of patients for whom data on "split" HLA specificities were available (n = 82 965, 47%) showed similar results to those for the total population (data not shown separately).

DWFG was defined as death in a patient for whom there was no previous report of a failed or lost graft. For each patient who died, date and cause of death was requested from participating centers at the time of quarterly follow-up requests. For 297 of the 16 781 patients who died, more than one cause of death was indicated; of those, 23 patients for whom cause of death was indicated as infection or cardiovascular disease together with a diagnosis of cancer were counted in the analysis as death from cancer and 34 patients who were reported as having died from a combination of cardiovascular factors and infection were counted as cardiovascular deaths. The remaining combinations of infection, cardiovascular or cancer with other causes of death were counted as death from infection, cardiovascular reasons or cancer, respectively. Patients who died after graft failure or removal of a failed graft were censored at the time of graft failure. Cumulative incidence rates of DWFG were computed using the Kaplan–Meier method and reported with standard error (SE) values. The influence of HLA-A + B + DR mismatches on mortality was tested using the log rank Mantel–Cox test with trend. Multivariable Cox regression was undertaken to account for the possible influence of the following confounding factors: year of transplant, number of transplant (first or retransplant), recipient and donor age, gender and race, preformed panel reactive antibodies, cold ischemia time, cytomegalovirus (CMV) status, original disease leading to transplantation, general evaluation of patient as a candidate for transplantation as judged by transplant center at time of transplantation (good, moderate or poor), cause of donor death, donor history of hypertension or increased risk donor for other reasons as judged by center at time of transplantation and immunosuppressive medication (type of calcineurin inhibitor [cyclosporine or tacrolimus], type of antimetabolite [azathioprine or mycophenolic acid], antibody induction and use of steroids). All confounders were suitably categorized and missing values were considered as a separate category. All listed confounders had a significant influence on DWFG in univariate analysis and were therefore included in the multivariable Cox regression model. With the exception of pretransplant CMV status and steroid use, all factors had a significant influence in the multivariable Cox model. Cox analysis was stratified according to the patient's geographical origin. For cumulative incidence of DWFG, we calculated hazard ratios (HRs) of confounders with 95% confidence interval (CI). Hospitalization during first posttransplant year was recorded at the time of 1-year follow-up for patients with a functioning graft at 1 year. Frequency of repeated hospitalizations or length or severity of infection were not considered in the analysis. Association of HLA class I and II mismatch with hospitalization was tested using logistic regression considering the same confounders as considered in analysis of DWFG and, in addition, considered geographical region as a confounder. P values below 0.05 were considered significant. The software package IBM SPSS Statistics version 20 was used.

Results

In total, data from 177 584 kidney transplants were analyzed. Patient demographics and baseline characteristics are shown in Table 1.

During the first posttransplant year, 7926 patients were reported to have died with a functioning graft, and a further 8855 patients were reported to have died with a functioning graft during the years 2–5. The incidence of DWFG during the first posttransplant year (Kaplan–Meier estimation) was 4.8% (SE 0.05%), and 7.7% (SE 0.08%) during posttransplant years 2–5 (approximately 2% per year).

Causes of DWFG differed during year 1 and years 2–5 ($p < 0.001$). In the first year posttransplant, infection was the most common cause (32.2%) followed closely by cardiovascular death (30.9%) whereas cardiovascular death became the most frequent cause of death during posttransplant years 2–5 (29.6%) followed by infection (16.4%; Figure 1). Cancer, which played only a minor role during the first posttransplant year (3.6%), became a relatively frequent reason for DWFG during the period years 2–5 (15.9%). The true proportion of deaths arising from the causes shown in Figure 1 is likely to be somewhat higher than reported because cause of death was not reported in nearly 20% of patients who died with a functioning graft (Figure 1).

There was a striking association between the number of HLA-A + B + DR mismatches and the proportion of patients with DWFG during year 1 posttransplant, which became less pronounced but remained statistically significant during years 2–5 (Figure 2).

The relationship between HLA mismatches and specific causes of DWFG was analyzed for the three most frequent categories, namely infection, cardiovascular death and cancer (Figure 3). During the first year after transplantation, the number of HLA mismatches showed a clear association with death because of infection or cardiovascular causes ($p < 0.001$ [Mantel–Cox with trend]) but not with death because of cancer ($p = 0.28$). During years 2–5 posttransplant, the association between HLA mismatches and death from infection or cardiovascular disease was far less marked but continued to be statistically significant (Figures 3A and B). Death because of cancer again showed no correlation with HLA mismatches during years 2–5 (Figure 3C). Prolonged follow-up to 10 years showed similar results as those shown for 5 years in Figure 3 (death because of infection: $p = 0.015$, cardiovascular death: $p = 0.023$; death because of cancer: $p = 0.14$).

Cox regression analysis in which multiple confounders were considered confirmed these results. For the first posttransplant year, the HR for death because of infection was on average 1.09 per HLA (A, B, DR) mismatch,

Table 1: Demographic and baseline characteristics, n (%)

Characteristic	Missing (%)	All patients n = 177 584	Death with a functioning graft	
			Year 1 n = 7926	Years 2–5 n = 8855
Geographic region	0			
Europe		129 998 (73)	5314 (67)	6299 (71)
North America		24 812 (14)	1065 (13)	1329 (15)
Other		22 774 (13)	1547 (20)	1227 (14)
Recipient age (years)	0.4			
<18		7394 (4)	167 (2)	95 (1)
18–49		92 699 (52)	2570 (33)	2815 (32)
50–59		44 490 (25)	2439 (31)	2742 (31)
≥60		32 358 (18)	2714 (34)	3154 (36)
Female recipients	0.0	67 952 (38)	2848 (36)	2959 (33)
Caucasian recipients	18.4[1]	126 472 (87)	5428 (83)	6407 (87)
Retransplants	0.0	25 673 (14)	1049 (13)	1156 (13)
Presensitized patients (PRA > 5%)	17.9	47 997 (33)	2323 (37)	2477 (34)
Cold ischemia time (h)	10.7			
≤24		127 170 (80)	5386 (77)	6168 (78)
25–36		27 207 (17)	1332 (19)	1461 (19)
>36		4279 (3)	240 (3)	261 (3)
Donor age (years)	0.8			
<18		18 638 (11)	653 (8)	727 (8)
18–49		94 353 (54)	3687 (47)	4376 (50)
50–59		36 210 (21)	1750 (22)	1859 (21)
≥60		27 048 (15)	1761 (22)	1820 (21)
HLA A + B + DR mismatches	0			
0		15 344 (9)	527 (7)	776 (9)
1		18 006 (10)	775 (10)	915 (10)
2		42 196 (24)	1759 (22)	2071 (23)
3		52 162 (29)	2317 (29)	2637 (30)
4		32 798 (18)	1608 (20)	1584 (18)
5		13 430 (8)	731 (9)	697 (8)
6		3648 (2)	209 (3)	175 (2)
Immunosuppressive therapy[2]	6.2			
Cyclosporine + azathioprine		58 607 (35)	2826 (39)	3398 (41)
Cyclosporine + MPA		36 631 (22)	1464 (20)	1761 (21)
Tacrolimus + MPA		30 714 (18)	1013 (14)	1206 (14)
CNI + other		31 993 (19)	1404 (19)	1635 (20)
No CNI		8223 (5)	608 (8)	366 (4)
Steroids		157 543 (95)	6955 (95)	7953 (95)
Antibody induction therapy		62 002 (37)	2570 (35)	2739 (33)

[1]Certain European countries do not allow registration of race.
[2]Intent to treat at time of transplantation.

whereas the corresponding HR for cardiovascular death was smaller at HR 1.04 (Table 2). When HLA class I (A, B) and II (DR) mismatches were considered as two separate confounders, Cox analysis revealed a predominant association of death with HLA class II mismatches. For cardiovascular death, a significant effect of HLA class I mismatches could not be shown, primarily because of the distribution of confounders such as recipient age, pretransplant cardiovascular risk and pretransplant diabetes. The influence of HLA class II mismatches on death because of infection reached an HR of 1.15 per mismatch (Table 2).

Immunosuppressive therapy as well as prophylaxis and treatment of infection and cardiovascular disease have undergone profound changes during the 20-year study period. We therefore deemed it important to ascertain that the findings of this analysis applied to patients transplanted during recent years. Transplants performed from 2005–2009 were analyzed separately. The association of HLA mismatch with death from infection or cardiovascular cause was striking even in this recent analysis period ($p < 0.001$ for both causes of death; Mantel–Cox with trend; Figure 4). Multivariable Cox regression analysis showed similar results as those of the total analysis shown in Table 2, namely an HR for death from infection of 1.09 per HLA mismatch (95% CI 1.03–1.17; $p = 0.006$) and a weaker effect for cardiovascular death which did not reach statistical significance (HR 1.05; CI 0.98–1.13; $p = 0.15$).

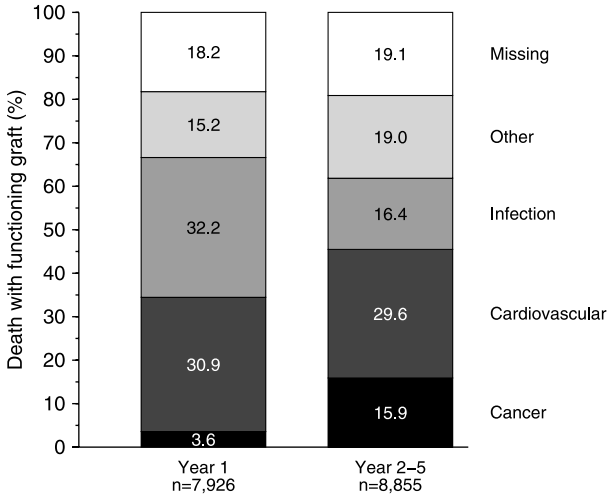

Figure 1: Cause of death with a functioning graft during year 1 and years 2–5 after kidney transplantation.

The association between HLA mismatches and hospitalization because of infection during posttransplant year one was examined separately for viral infections and bacterial infections (there were too few cases with fungal infection for meaningful analysis). Information as to whether death from infectious disease was because of viral or bacterial infection is not recorded by the CTS, but the type of infection recorded for hospitalization because of infection during the first posttransplant year is captured for patients who survive with a functioning graft to the end of year 1. HLA mismatches were associated with hospitalization because of viral ($p < 0.001$) or bacterial infection ($p = 0.002$; Figure 5). Paralleling the results of the analysis of DWFG, HLA class II mismatches proved more influential than class I mismatches in multivariable logistic regression analysis. The association of HLA class II mismatches with hospitalization because of viral infection showed an odds ratio (OR) of 1.09 (CI 1.03–1.15; $p = 0.004$) per mismatch for class II and OR 1.04 (CI 1.01–1.08; $p = 0.022$) per mismatch for class I. The corresponding results for hospitalization for bacterial infection were OR 1.07 (CI 1.02–1.13; $p = 0.011$) for class II and OR 1.01 (CI 0.97–1.04; $p = 0.68$) for class I. Patients who died during the first year were of course not included in this part of the analysis in which hospitalization was analyzed in patients who had a functioning graft at year one. Because death during the first year was related to HLA match, the association of HLA matches with hospitalization for infection in the remaining patients further supports the role of HLA.

Discussion

The pattern of DWFG in this large cohort of kidney transplant recipients appears compatible with other reports. In our population, the proportion of deaths because of infection, cardiovascular disease and malignancy was generally similar to those reported in a recent analysis of USRDS data from 2005–2009 (2). In that analysis, the proportion of deaths with a functioning graft during follow-up was reported to be 20.9% for infection, 29.7% for cardiovascular

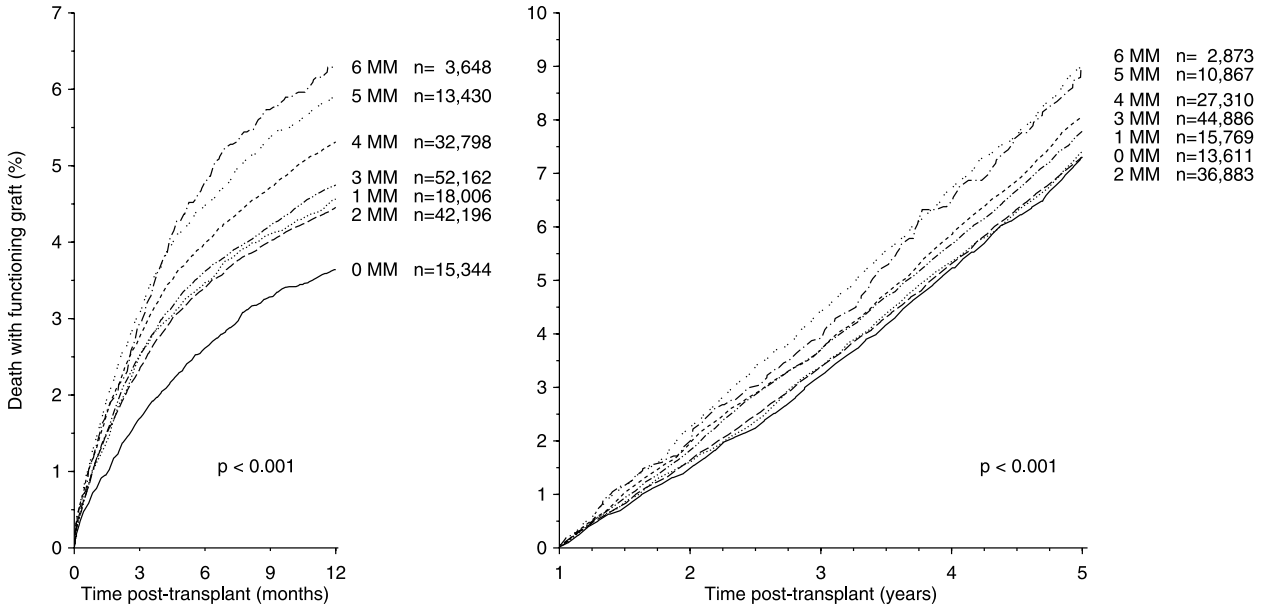

Figure 2: Cumulative rate of death with a functioning graft during year 1 and years 2–5 after kidney transplantation according to the number of HLA-A + B + DR mismatches.

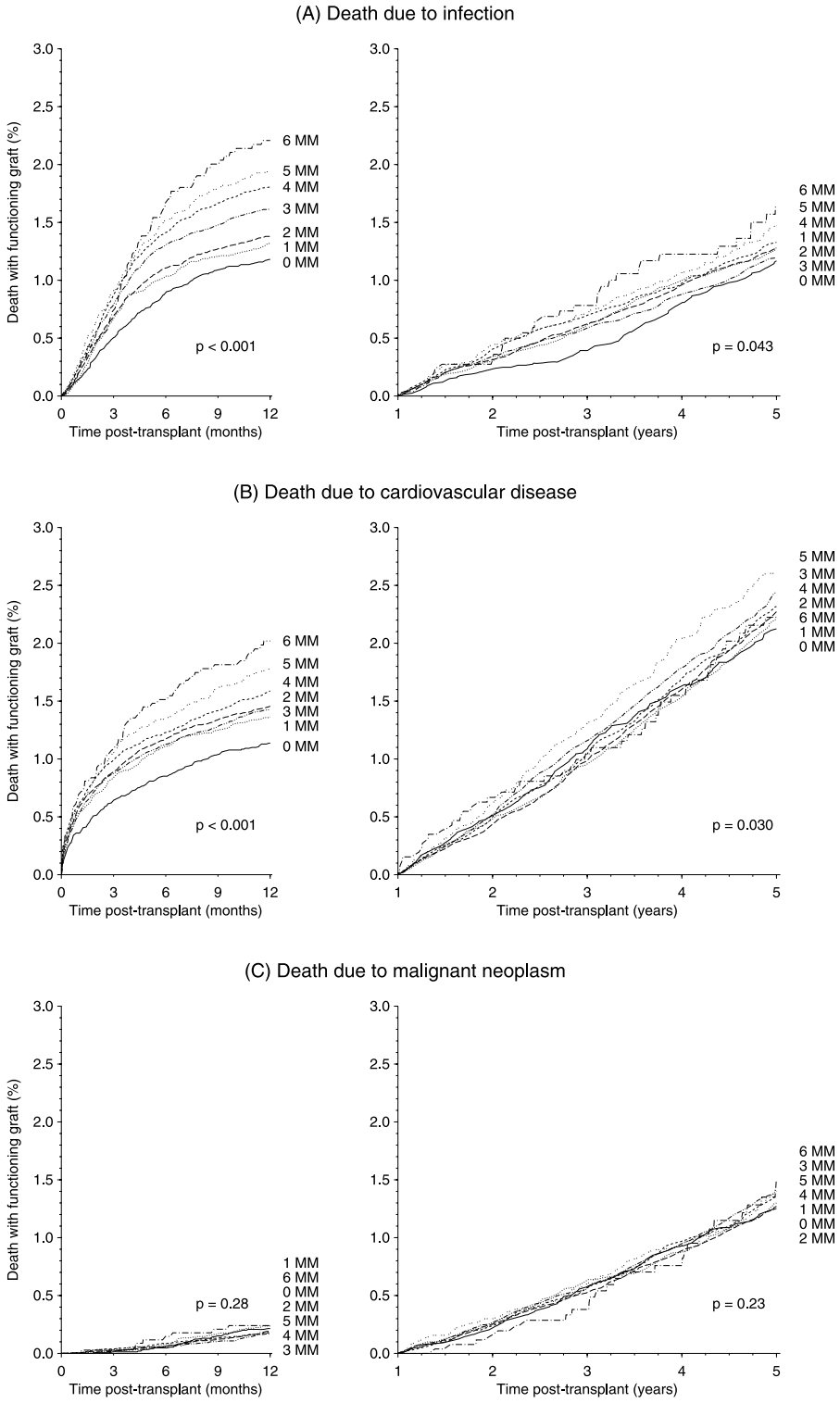

Figure 3: Cumulative rate of death with a functioning graft during year 1 and years 2–5 after kidney transplantation because of (A) infection, (B) cardiovascular disease and (C) malignant neoplasm according to the number of HLA-A + B + DR mismatches.

disease and 9.3% for malignancy, with no differentiation of incidence according to time posttransplant. Similar to our study, the cause of DWFG was unknown in 18% of cases. Our finding that infection-related deaths became less common after the first year posttransplant, however, conflicts with a previous analysis of UNOS data (1), a difference that may be because of advances in management between the time periods in question (1990–2009 in this study compared to 1988–1999 in the UNOS analysis). The preponderance of cardiovascular mortality after the first

Table 2: Hazard ratios (HR) of Cox regression analysis for death with a functioning graft because of infection or cardiovascular disease during the first year after kidney transplantation

	Death because of infection			Death because of cardiovascular disease		
Confounder	HR	95% CI	p-Value	HR	95% CI	p-Value
A + B + DR						
Per MM	1.09	1.05–1.12	<0.001	1.04	1.01–1.07	0.005
0 MM	1 (Ref)			1 (Ref)		
1 MM	1.01	0.82–1.23	0.95	1.17	0.96–1.44	0.12
2 MM	1.06	0.89–1.27	0.50	1.28	1.08–1.53	0.005
3 MM	1.25	1.06–1.48	0.010	1.23	1.04–1.46	0.017
4 MM	1.35	1.13–1.61	0.001	1.30	1.09–1.56	0.004
5 MM	1.37	1.11–1.67	0.003	1.32	1.07–1.62	0.010
6 MM	1.53	1.15–2.02	0.003	1.46	1.09–1.94	0.011
A + B (Class I)						
Per MM	1.05	1.01–1.10	0.007	1.02	0.98–1.06	0.39
0 MM	1 (Ref)			1 (Ref)		
1 MM	0.98	0.83–1.16	0.85	1.21	1.02–1.42	0.025
2 MM	1.05	0.90–1.22	0.57	1.12	0.96–1.31	0.16
3 MM	1.13	0.97–1.33	0.12	1.17	0.99–1.37	0.064
4 MM	1.17	0.97–1.42	0.10	1.16	0.95–1.41	0.15
DR (Class II)						
Per MM	1.15	1.09–1.23	<0.001	1.10	1.03–1.17	0.003
0 MM	1 (Ref)			1 (Ref)		
1 MM	1.23	1.12–1.34	<0.001	1.10	1.00–1.20	0.043
2 MM	1.29	1.14–1.47	<0.001	1.19	1.04–1.35	0.011

Ref = reference.
All confounders listed in Methods were included; results of 2 Cox-model computations as indicated by horizontal separation line.

year following kidney transplantation was a consistent finding in both reports (1).

HLA mismatches showed a highly significant association with death because of infection or cardiovascular disease during the first year after kidney transplantation, which persisted but was far less marked during years 2–5. We observed no association between HLA mismatches and cancer-related mortality in either time period. Notably, the proportion of patients who died with a functioning graft

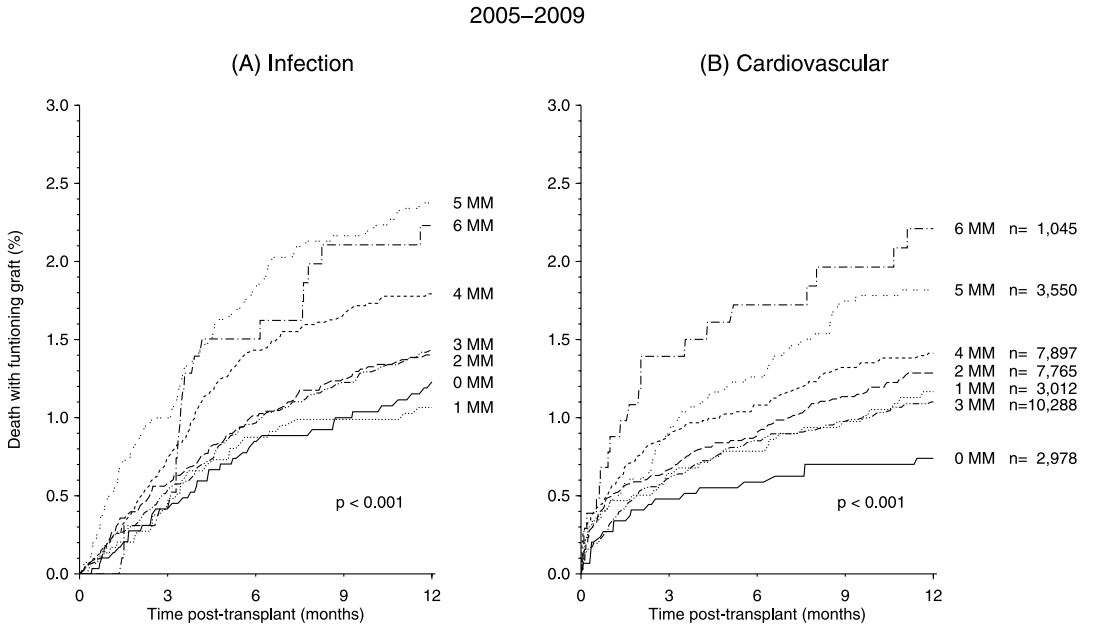

Figure 4: Transplants performed 2005–2009. Cumulative rate of death with a functioning graft during year 1 after kidney transplantation because of (A) infection or (B) cardiovascular disease according to the number of HLA-A + B + DR mismatches.

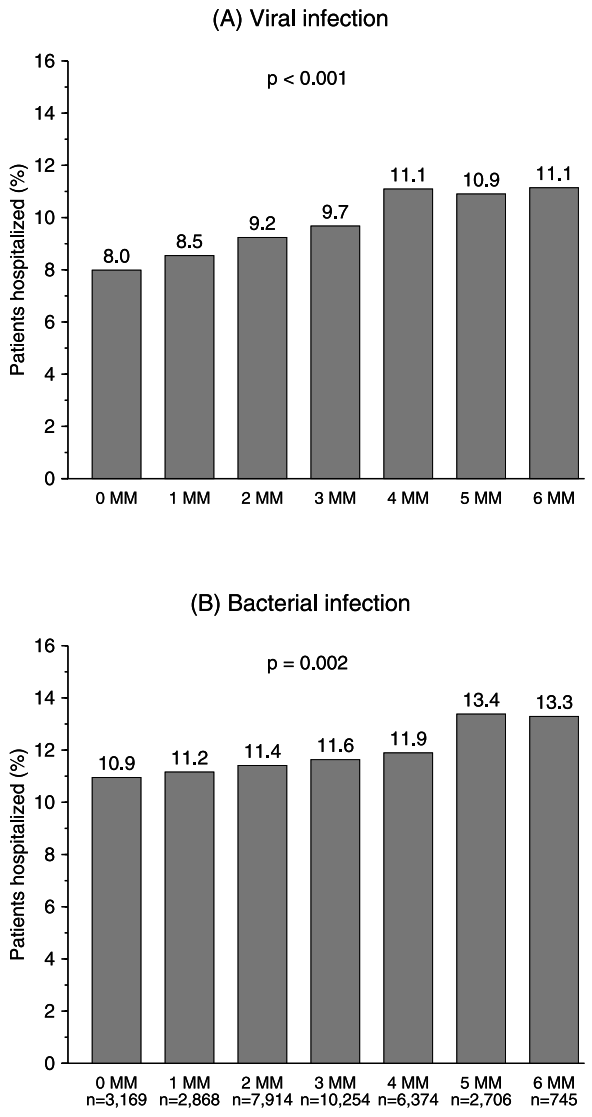

Figure 5: Percentage of patients hospitalized during year 1 after kidney transplantation because of (A) viral infection, (B) bacterial infection according to the number of HLA-A + B + DR mismatches among patients with a functioning graft at one year posttransplant. P values according to chi-square test for linear trend.

was approximately twice as high among recipients who received a transplant with six HLA mismatches versus those with a zero antigen mismatch (Figure 2). The relation between HLA matching and DWFG was graded according to the extent of mismatching: the more mismatches, the higher the rate of death. Elsewhere, an analysis of UNOS data from kidney transplants performed during 1994–2004 assessed potential contributing factors to the risk of DWFG in a logistic regression analysis (1). Over a 5-year follow-up period, DWFG was compared in patients with 3–4 or 5–6 HLA mismatches versus 0–2 mismatches. Under those conditions, no statistically significant association between HLA mismatch and DWFG was observed in recipients of deceased-donor kidney grafts, but it is relevant that the OR increased with higher numbers of HLA mismatches (OR 0.97 [95% CI 0.86–1.10] with 3–4 mismatches, OR 1.06 [95% CI 0.92–1.21] with 5–6 mismatches). Our current findings are consistent with earlier reports from the CTS database that there is a graded relationship between the number of HLA mismatches and maintenance immunosuppression dose levels (13) as well as the requirement for rejection therapy (14). A limitation of our study is that, whereas dosage of immunosuppressive maintenance therapy is recorded at 1 year posttransplant, detailed information on dose administered for rejection treatment or cumulative dose of immunosuppressive drugs administered during the first posttransplant year is not available in the CTS database and could therefore not be analyzed. Although an observational study of this type cannot explore the mechanisms of an observed relationship, the most likely explanation for the association of HLA mismatches and DWFG is a need for more intensive immunosuppression in response to a higher rate of rejection episodes. It is possible, however, that a generally stronger anti-graft immune response in HLA mismatched transplants might in turn influence the progression of cardiovascular disease or vulnerability to infection. Our findings suggest that prospective HLA matching of wait-listed kidney transplant candidates and donor organs could potentially reduce the rate of DWFG by ameliorating the toll of cardiovascular and infectious mortality. Although the incidence of DWFG is low (5% of patients during the first year posttransplant and 2% per year during the years 2–5), it is the most critical endpoint from the viewpoint of the patient. Moreover, this report should be viewed alongside other evidence regarding the influence of HLA mismatches on outcomes other than kidney allograft survival: previous analyses of the CTS database have shown HLA match to have a significant impact on the incidence of posttransplant lymphoma (13), and posttransplant osteoporosis and hip fracture (15). To these we can now add a significant association between HLA mismatches and DWFG because of infection or cardiovascular disease.

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Haifa, Halifax, Halle, Hamilton (2), Hann-Münden, Hannover, Hartford, Heidelberg (2), Helsinki, Homburg, Hong Kong (7), Innsbruck, Istanbul (2), Izmir (2), Jena (2), Jerusalem, Kaiserslautern, Kansas City (4), Karachi, Katowice, Kaunas, Kent, Kiel, L'Aquila, Lausanne, Lecce, Leeds, Leicester, Leiden, Leipzig, Leuven (2), Liege, Lima, Limoges, Linz (2), Liverpool, Ljubljana, London (8), Louisville, Lübeck, Lyon, Maastricht, Madrid (2), Mainz, Malmo-Lund, Manchester, Manila, Mannheim, Mar del Plata, Marburg, Martin, Medellin (2), Melbourne (5), Mexico City, Milan (4), Modena, Moscow, Münster, Munich (2), Nancy (2), Nantes, Naples, Neiva, New Orleans, New York (2), Newcastle Australia, Newcastle u Tyne (4), Nijmegen, Nottingham, Novara, Oklahoma City, Omaha, Orlando, Osijek, Oviedo, Oxford, Padua (2), Palermo (3), Pamplona, Panama, Parma, Pato Branco, Pavia, Pecs, Perth, Perugia, Phoenix, Pisa, Plymouth, Plzen, Poitiers, Portland, Porto Alegre (2), Portsmouth, Prague, Quebec, Regensburg, Reggio di Calabria, Reims, Rennes, Ribeirao Preto, Rijeka, Rio de Janeiro (2), Rome (7), Rosario (2), Rostock (2), Rotterdam (2), Santa Fe, Santander, Santiago, Sao Paulo (4), Sassari, Seoul, Sheffield, Siena, St. Etienne, St. Gallen, Stanford, Stoke on Trent, Stony Brook, Strasbourg, Stuttgart, Sydney (11), Szeged, Tel Aviv, Treviso, Tübingen, Turin (2), Udine, Ulm, Uppsala, Utrecht (2), Valdivia, Valencia (3), Valhalla, Varese, Verona, Vicenza, Vilnius, Wellington, Wichita, Winnipeg, Würzburg, Zagreb, Zurich.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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