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ORIGINAL ARTICLE

Human leukocyte antigen matching in heart transplantation: systematic review and meta-analysis

David Ansari,[1] Dragan Bućin[2] and Johan Nilsson[1]

1 Division of Cardiothoracic Surgery, Department of Clinical Sciences Lund, Lund University and Skane University Hospital, Lund, Sweden
2 Division of Nephrology and Transplantation, Department of Clinical Sciences in Malmö, Lund University and Skåne University Hospital, Malmö, Sweden

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Correspondence
Johan Nilsson MD, PhD, Division of Cardiothoracic Surgery, Department of Clinical Sciences Lund, Lund University and Skåne University Hospital, 221 85 Lund, Sweden.
Tel.: +46 46 17 38 24;
fax: +46 46 15 86 35;
e-mail: johan.nilsson@med.lu.se

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Summary

Allocation of donors with regard to human leukocyte antigen (HLA) is controversial in heart transplantation. This paper is a systematic review and meta-analysis of the available evidence. PubMed, Embase, and the Cochrane Library were searched systematically for studies that addressed the effects of HLA matching on outcome after heart transplantation. Fifty-seven studies met the eligibility criteria. 34 studies had graft rejection as outcome, with 26 of the studies reporting a significant reduction in graft rejection with increasing degree of HLA matching. Thirteen of 18 articles that reported on graft failure found that it decreased significantly with increasing HLA match. Two multicenter studies and nine single-center studies provided sufficient data to provide summary estimates at 12 months. Pooled comparisons showed that graft survival increased with fewer HLA-DR mismatches [0–1 vs. 2 mismatches: risk ratio (RR) = 1.09 (95% confidence interval (CI): 1.01–1.19; $P = 0.04$)]. Having fewer HLA-DR mismatches (0–1 vs. 2) reduced the incidence of acute rejection [(RR = 0.81 (0.66–0.99; $P = 0.04$)]. Despite the considerable heterogeneity between studies, the short observation time, and older data, HLA matching improves graft survival in heart transplantation. Prospective HLA-DR matching is clinically feasible and should be considered as a major selection criterion.

Introduction

In the past three decades, there has been improvement in survival after heart transplantation due to advancements in postoperative intensive care and surgical technique, and more effective immunosuppressive strategies. However, graft failure still remains a major problem [1].

In the field of kidney transplantation, there is strong support for the beneficial effect of minimizing human leukocyte antigen (HLA) mismatch between donor and recipient [2,3]. This has led to improvement in the long-term prognosis of kidney transplant patients [4,5]. In other fields of organ transplantation, for example liver and lung transplantation, HLA mismatch has shown unfavorable outcomes [6–12].

Basic immunological incompatibility between humans is a well-known risk factor for premature death after heart transplantation. The HLA antigens are primary targets of the specific immune response in organ transplantation through their interaction with T-cell receptors. T-cell co-receptors CD8 and CD4 interact with HLA class I (A, B, and C) and HLA class II (DR, DQ, and DP) antigens, respectively [13,14].

The relationship between HLA matching and outcome in heart transplantation has been the subject of several studies, most of which were published before 2000 [15–17]. Due to limitation in ischemic time, extensive HLA antigen polymorphism, donor shortages, and logistics, transplantation between HLA-identical donor–recipient pairs and well-matched transplants has not been possible in many cases [18]. The impact of HLA matching on the outcome of heart transplantation has therefore been difficult to adequately analyze. Observational studies from the early 1990s have found that HLA-A, -B, and -DR mismatching significantly reduces 3-year graft survival in heart transplantation [19]. However, other studies have not been able to show any

significant correlation between HLA mismatch and graft or patient survival [20,21]. The HLA typing techniques used today have made it possible to determine HLA type more quickly [22]. This makes HLA matching feasible in the clinical setting and makes interpretation of the result of greater importance.

The aim of this study was to evaluate the efficacy of HLA matching in heart transplantation by performing a systematic review and meta-analysis of the available evidence.

Methods

A systematic literature search was conducted using PubMed (inception to January 25, 2013), Embase, and the Cochrane Library using the search terms "heart transplantation" and "HLA." Specific guidelines outlined in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) were followed [23]. Only original articles in English were considered. All the reference lists in the articles selected were carefully screened for any further articles not identified in the initial search.

Study selection

The titles and abstracts of all studies identified by the initial search were reviewed, and irrelevant studies were excluded. The full text of potentially relevant articles was obtained. Then, full-text articles were assessed to determine whether they met the inclusion criteria of this review. Any discrepancies in inclusion were resolved by discussion between the reviewers. The following data were extracted from each article that was included, using a data-extraction sheet: publication year, sample size, study design, patient characteristics, type of intervention, HLA data, follow-up, and outcomes. Disagreement was resolved by discussion between the reviewers; if no agreement could be reached, an additional reviewer made the final decision. Meta-analysis was performed for trials that had the same outcome and shared common follow-up, HLA analyzed, number of mismatches, and statistical analysis. Meta-analysis with fewer than three studies was not carried out due to low power. The methodological quality of the studies was described using the Newcastle–Ottawa Scale, which was designed for assessment of the quality of nonrandomized studies in meta-analyses. It scores potential sources of bias and variation in cohort studies regarding selection, comparability, and outcome. Publication bias was assessed with funnel plots. Funnel plot asymmetry indicated that results were subject to reporting publication bias, whereas symmetry indicated a lack of bias.

Inclusion criteria

Articles reporting the outcome of adult patients undergoing primary heart transplantation with regard to HLA matching were included. Case series were included only if the authors had reported the outcome for consecutive patients.

Exclusion criteria

Publications reporting pediatric studies were excluded. Studies on HLA antibodies and studies on HLA without matching were excluded. Irrelevant topics and studies on organ transplantation other than heart were excluded. Articles with no original data, such as reviews and technical descriptions, were also disregarded. Conference abstracts were excluded. Duplicate reports were removed. Outcome measures were graft rejection, graft failure, patient survival, and cardiac allograft vasculopathy (CAV). CAV was defined as atherosclerosis or luminal narrowing diagnosed with angiography.

Statistical analysis

Outcomes of interest were tabulated and shown in descriptive and individual form. Meta-analysis was directed at identification of differences in outcomes between different degrees of HLA mismatch. Data were extracted with the software "Engauge 4.0" (Free Software Foundation) from survival curves if they were not shown in articles directly. The software package Review Manager (RevMan 5.2) provided by The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, was used for analysis. Risk ratio (RR) with 95% confidence interval (CI) was calculated for dichotomous variables. The random-effects model [24] was used to account for heterogeneity. Heterogeneity was explored using the chi-squared test with significance set at $P < 0.100$ and quantified [25] using I^2 with a maximum value of 50% identifying low heterogeneity.

Results

In the initial literature search, we identified 1035 studies from PubMed, 2688 from Embase, and 21 from the Cochrane Library. Figure 1 outlines the search strategy. Screening of references did not provide any additional articles. Fifty-seven studies were included in the final analysis [15–21,26–75]. Only twelve studies were of multicenter design [15,16,19–21,68–74]. Forty-five of the studies were single-center [17,18,26–67,75]. Mean follow-up was 3.4 years, and 13 studies reported follow-up of 5 years or more. With few exceptions, the immunotherapy treatment protocol consisted of triple therapy with cyclosporine (CsA), azathioprine (Aza), and steroids (ste). Details of the study designs and outcomes are given in Tables 1 and 2.

Graft rejection

The only multicenter study on graft rejection was published by Jarcho *et al.* [69] and included 1190 patients from 27

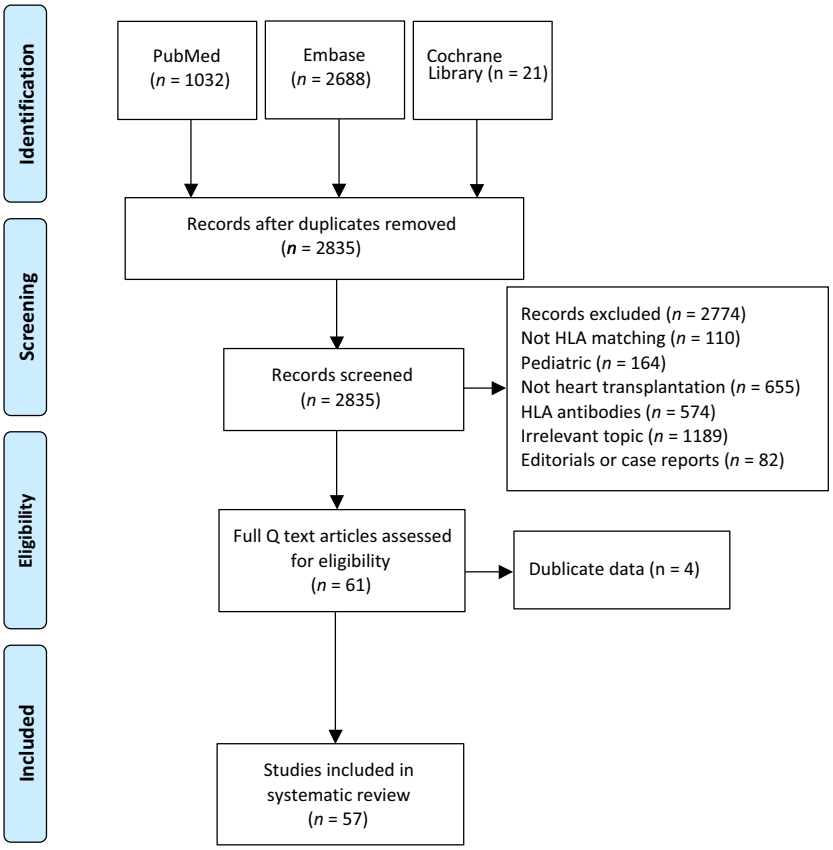

Figure 1 PRISMA flow diagram.

institutions participating in the Cardiac Transplant Research Database. By multivariable analysis, it was found that the number of HLA-A, -B, and -DR mismatches was a risk factor for time to first rejection ($P = 0.013$), but not in black recipients. Zero, one, or two mismatches were associated with a 54% freedom from rejection at 1 year, as opposed to 36% for three or more mismatches ($P = 0.02$). In addition, the number of HLA-DR mismatches, younger recipient age, female gender of both donor and recipient, and the use of induction therapy were associated with cumulative rejection frequency in the first year after transplantation ($P = 0.04$ for HLA-DR mismatch). Of the single-center studies, the majority (25/33) found a significant association between the degree of HLA mismatch and graft rejection.

Cardiac allograft vasculopathy

To date, no multicenter studies have evaluated the relationship between HLA mismatch and CAV. Of the single-center studies, only a minority (4/11) found a significant effect of HLA mismatch on CAV. The degree of atherosclerosis or luminal narrowing was specified only in a small number of studies.

Graft survival

Opelz and coworkers published three multicenter studies investigating the role of HLA matching on graft survival. In the first report, involving 2000 patients, they reported a significant correlation between HLA-B, DR matching, and graft survival at 1 year (88% for <2 mismatches with HLA-B, DR vs. 78% for ≥2 mismatches; $P = 0.05$) [15]. In the second study, they found that there was a strong correlation between the 3-year rate of graft survival and HLA compatibility. Graft survival decreased from 83% for the 128 patients with no mismatches or only one mismatch to 76% for the 439 patients with two mismatches, and to 71% for the 7764 patients with three to six mismatches ($P < 0.001$). The correlation remained significant after adjusting for multiple covariates ($P = 0.005$) [19]. The association with graft survival was less impressive when mismatches at the individual HLA loci (A, B, and DR) were investigated, and it remained significant only for HLA-DR. The third study included black recipients only, and no significant effect of HLA mismatch on graft failure was seen in the 103 patients investigated [70]. Thompson *et al.* [72] noted a clear effect of HLA-DR matching on

Table 1. Characteristics of the multicenter studies included.

Reference	Year	*n*	HLA locus analysis*	Resolution	Follow-up (y)	Immunotherapy	Registry	Stat.	Outcome
Hosenpud *et al.* [68]	1996	10 752	A, B, DR, A+B+DR	Serology/ DNA	3	–	UNOS	M	Progressive reduction in mortality risk at 3 years for greater matching, primary benefit at HLA-A and DR loci.
Jarcho *et al.* [69]	1994	1190	A+B+DR, A, B, DR	Serology/ DNA	2.5	–	CTRD	M	Number of HLA mm correlates with time to first rejection (not in blacks); HLA-DR associated with cumulative rejection frequency; no correlation with graft failure; HLA mm correlates with rejection-related death at 2 years.
Mascaretti *et al.* [16]	1997	661	A+B+DRB1, DRB1, A+B	DNA	3	A.L.G	NITp	M	No significant correlation with 1- and 3-year patient survival.
Opelz *et al.* [15]	1989	2000	A+B, DR, B+DR	Serology/ DNA	1	CsA, Aza, Ste	CTS	M	Significant correlation between HLA-B, -DR and graft survival at 1 year.
Opelz *et al.* [19]	1994	8331	A+B+DR, A, B, DR, A+B	Serology/ DNA	3	CsA, Aza, Ste	CTS	M	3-year graft survival correlates significantly with HLA mm.
Opelz *et al.* [70]	1997	103	A+B+DR, B+DR	Serology/ DNA	3	–	CTS	M	No significant correlation with graft survival in black recipients.
Park *et al.* [71]	1997	336	A+B, DR	Serology	4.4	CsA, Aza, Ste		U	Modestly improved 10-year patient survival for HLA-A, -B compatibility (Caucasians), though not significant ($P = 0.06$).
Poli *et al.* [20]	1992	168	A+B+DR, DR	DNA	1	CsA, Aza, Ste, A.L.G	NITp	U	No significant correlation with patient survival.
Poli *et al.* [21]	1995	358	A+B, DRB1	DNA	2	CsA	NITp	M	No significant correlation with graft survival.
Thompson *et al.* [72]	1998	1927	DR, A+B+DR	–	3	–	SEOPF		Clear effect of HLA-DR matching on 1- and 3-year graft survival.
Thompson *et al.* [73]	2000	14 535	A, B, DR, A+B, A+B+DR	Serology/ DNA	3	CsA, Aza, Ste	UNOS	M	3-year graft survival superior for HLA-A, -B, and -DR matching. When analyzed separately, 1- and 3-year graft survival directly related to the number of HLA-DR mm.
Valeri *et al.* [74]	1990	92	DR, B+DR	Serology	3	CsA.		U	HLA-B and -DR matching have a positive effect on 1- and 3-year patient survival.

HLA, human leukocyte antigen; UNOS, United Network for Organ Sharing, all centers in USA; CTRD, Cardiac Transplant Research Database, 27 centers in USA; NITp, Northern Italy Transplant program, 5 centers; CTS, Collaborative Transplant Study, centers worldwide; SEOPF, Southeastern Organ Procurement Foundation; M, multivariable (Cox proportional hazards regression); U, univariable; mm, mismatch; CsA, cyclosporine; Aza, azathioprine; A.L.G, antilymphocyte globulin; Ste, steroids.

*HLA-A, B, DR: each locus was analyzed separately, 0–2 mm. HLA A+B: A and B loci were analyzed together, 0–4 mm. HLA B+DR: B and DR loci were analyzed together, 0–4 mm. HLA A+B+DR: all loci were analyzed together, 0–6 mm.

1- and 3-year graft survival in their survey of 1927 cardiac transplants performed by Southeastern Organ Procurement Foundation centers. In another study by Thompson *et al.* [73], in a survey of 14 535 heart transplant recipients in the United Network of Organ Sharing Transplant Registry, they found a beneficial effect of HLA-A, -B, and -DR compatibility on 3-year graft survival. When analyzed separately, 1- and 3-year graft survival values were directly related to the number of shared HLA-DR antigens. In contrast, the multicenter study by Jarcho *et al.* [69] did not show any significant association despite the probability of rejection-related death or re-transplantation by 2 years being 0% with no, one, or two HLA mismatches and 5% with three to six mismatches ($P = 0.14$). The small multicenter study by Poli *et al.* [21] involving 358 heart transplant patients did not find any relationship between HLA locus mismatch and graft survival either. Of the single-center studies, the majority (9/11) found a significant correlation between HLA mismatch and graft failure.

Table 2. Single-center studies.

Reference	Year	*n*	HLA locus analysis*	Resolution	Immunotherapy	Follow-up (y)	Statistical model	Outcome
Almenar *et al.* [26]	2005	243	A+B+DR	Serology	CsA, MMF/Aza, Ste, Tac(s)	4.7	Univariable	Associated with PS (inverse relationship). No effect on GR and GS.
Arbustini *et al.* [27]	1997	429	A, B, DR, A+B, A+B+DR	Serology	CsA, Aza, Ste	3.8	Multivariable (Poisson)	HLA-B associated with CAV.
Aziz *et al.* [28]	1998	249	A, B, DR	Serology/ DNA	CsA, Aza, Ste	–	Univariable	HLA-DR associated with GR. No effect on CAV.
Baan *et al.* [29]	1991	118	A, B, DR, B+DR	–	–	0.5	Univariable	HLA-B and -DR associated with GR.
Botha *et al.* [30]	1969	5	–	–	Aza, Ste, A.L.G	–	None	No outcome analysis.
Brunner La-Rocha *et al.* [31]	1996	161	A+B+DR	–	CsA, Aza, Ste	3	Multivariable (logistic regression)	Associated with GR.
Carrier *et al.* [32]	1990	20	A+B	–	CsA, Aza, Ste. ATG	0.1	Univariable	No effect on GR.
Cocanougher *et al.* [33]	1993	160	A+B+DR, B+DR	Serology	CsA/OKT3, Aza, Ste	–	Univariable	Associated with CAV. HLA-A, -B, and -DR associated with PS.
Cochrane *et al.* [34]	1992	55	A,B, DR	–	CsA, Aza, Ste	0.5	Multivariable (Cox)	HLA-DR associated with GR.
Costanzo-Nordin *et al.* [35]	1993	195	A, B, DR	Serology	CsA, Aza, Ste	3	Univariable	HLA-DR associated with GR. No effect on PS.
De Mattos *et al.* [17]	1994	132	DR	Serology	CsA/OKT3, Aza, Ste	7	Univariable	HLA-DR associated with GR and GS. No effect on CAV.
DiSesa *et al.* [36]	1990	51	A+B, A+B+DR	–	CsA, Aza, Ste	2.8	Univariable	HLA-A or -B associated with GR.
DiSesa *et al.* [37]	1994	31	A+B, A, B, DR	Serology	–	–	Univariable	HLA-A+B associated with GR.
Fieguth *et al.* [38]	1991	61	A, B, DR, B+DR	–	CsA, Aza, Ste	2.8	Univariable	HLA-B+DR or B associated with GR. No effect on CAV.
Foerster *et al.* [39]	1988	51	A, B, C, DR	Serology	CsA, Aza, Ste	1.1	Multivariable (Cox)	HLA-DR associated with GR and GS.
Foerster *et al.* [40]	1991	100	A, B, DR	Serology	CsA, Aza, Ste	2.2	Multivariable (Cox)	HLA-DR associated with GS. No effect on PS.
Foerster *et al.* [41]	1992	100	A, B, DR	–	CsA, Aza, Ste	5	Multivariable (Poisson)	HLA-B+DR associated with GR.
Frist *et al.* [42]	1987	164	A+B, A, B	Serology	CsA, Aza, Ste	5	Univariable	HLA-A+B or -A associated with PS. No effect on GR.
Hollander *et al.* [43]	2013	53	A+B+DR	–	CsA, MMF, Ste, Sir(s), Tac(s),	3	Univariable	No effect on GR.
Hornick *et al.* [44]	1997	534	A, B, DR, A+DR, A+B+DR	Serology/ DNA	CsA, Aza, Ste	3	Univariable	No effect on CAV.
Kaczmarek *et al.* [18]	2006	240	A+B+DR, A, B,DR	Serology/ DNA	CsA, Aza, MMF, Tac, Ste	5.9	Multivariable (Cox)	HLA-DR associated PS. No effect on CAV.
Keogh *et al.* [46]	1995	183	A, B, DR	Serology/ DNA	CsA, Aza, Ste	4	Univariable	HLA-A, -B, or -DR associated with GR.
Kerman *et al.* [47]	1994	448	A+B, DR	Serology	CsA, Aza, Ste	5	Univariable	HLA-A+B or -DR associated with GR. HLA-A+B associated with CAV (inverse relationship).

Table 2. continued

Reference	Year	*n*	HLA locus analysis*	Resolution	Immunotherapy	Follow-up (y)	Statistical model	Outcome
Khagani *et al.* [45]	1989	353	A, B, DR, DQ, DRW52/53	Serology	CsA, Aza.	2	Univariable	HLA-DR associated with GS.
Kirklin *et al.* [48]	1992	229	A+B+DR	Serology	CsA, Aza, Ste	10	Univariable	Associated with GR.
Laufer *et al.* [49]	1989	43	A, B, DR, B+DR, A+B+DR	Serology	CsA, Aza, Ste	0.5	Multivariable (logistic regression)	HLA-B+DR associated with GR.
Leivestad *et al.* [50]	1996	208	A, B, DR	Serology/DNA	CsA, Aza, Ste	5	Multivariable (Cox)	HLA-DR associated with GR.
Ouwehand *et al.* [51]	1994	118	A, B, DR, B+DR	Serology	CsA, Ste	0.5	Univariable	HLA-B+DR associated with GR.
Pfeffer *et al.* [52]	1988	37	A, B, DR	Serology	CsA, Aza, Ste	0.3	Univariable	HLA-DR associated with GR.
Pollack *et al.* [53]	1990	113	A+B+DR	Serology	CsA/OKT3, Aza, Ste	5.5	Univariable	HLA-A+B+DR associated with GR. No effect on CAV and PS.
Radovancevic *et al.* [54]	1991	167	A+B+DR, A, B, DR	Serology	CsA, Aza, Ste	2.9	Univariable	HLA-A or total HLA mm associated with CAV (inverse relationship).
Raffoux *et al.* [55]	1987	266	A+B, A+B+DR, DR	Serology	CsA, Aza, Ste	2	Univariable	HLA-A+B or HLA-A+B+DR associated with GS.
Rementeria *et al.* [56]	1997	165	A+B+DR	–	–	0.5	Univariable	Associated with GR.
Shakin-Eshleman *et al.* [57]	1990	82	A, B, DR, A+B, A+DR, A+B+DR, B+DR, Bw4/6, Bw4/6 + DR, DR52/53	Serology	CsA, Aza, Ste	1	Univariable	No effect on GR and PS.
Sheldon *et al.* [58]	1992	127	B+DR, DR	Serology/ DNA	–	5	Univariable	No effect on GR and PS.
Sheldon *et al.* [59]	1994	165	A, B, DR	Serology/ DNA	CsA, Aza, Ste	6	Univariable	HLA-B or -DR associated with GR.
Sheldon *et al.* [60]	1999	261	A, B, DR, A+B, A+B+DR	Serology/ DNA	CsA, Aza, Ste	8	Multivariable (Cox)	HLA-DR associated with GR. HLA-A+B or HLA-DR associated with GS.
Smith *et al.* [61]	1995	1135	A, B, DR	Serology/ DNA	–	10	Univariable	HLA-DR associated with GR and GS.
Stempfle *et al.* [62]	1995	24	A+B+DR	Serology/ DNA	CsA, Aza, Ste	–	Univariable	Associated with CAV. No effect on GR.
Suberbielle *et al.* [63]	1994	202	A+B+DR, DR, A+B	Serology	CsA, Aza, Ste, ATG	1	Univariable	No effect on GR and GS.
Taylor *et al.* [64]	1997	477	A, A+B, A+B+DR	Serology/ DNA	CsA, Aza, Ste	5	Multivariable (Cox)	HLA-A associated with GS (inverse relationship).
Tenderich *et al.* [65]	2007	923	A, B, C, DQ	Serology	CsA, Aza, Tac, MMF, Ste	10	Multivariable (Cox)	No effect on PS.
Yacoub *et al.* [66]	1987	204	A, B, Bw4/6, DR, DQ, DRw52/w53, B+DR, B+DRw52/w53	Serology	CsA, Aza	2	Univariable	HLA-DR associated with GS.
Zerbe *et al.* [75]	1988	242	A, B, DR	Serology	–	–	Univariable	Associated with GR.

Table 2. continued

Reference	Year	*n*	HLA locus analysis*	Resolution	Immunotherapy	Follow-up (y)	Statistical model	Outcome
Zerbe *et al.* [67]	1991	413	A+B+DR+DQ	Serology	CsA, Aza, Ste	0.3	Multivariable (Cox)	Associated with GR.

CAV, cardiac allograft vasculopathy; Cox, cox proportional hazards regression; HLA, human leukocyte antigen; mm, mismatch; GR, graft rejection; GS, graft survival; PS, patient survival; CsA, cyclosporine; Aza, azathioprine; A.L.G, antilymphocyte globulin; Ste, steroids; ATG, antithymocyte globulin; OKT3, orthoclone OKT3; Tac, tacrolimus; Sir, sirolimus; s, small proportion of patients.
*HLA-A, B, DR: each locus was analyzed separately, 0–2 mm. HLA A+B: A and B loci were analyzed together, 0–4 mm. HLA B+DR: B and DR loci were analyzed together, 0–4 mm. HLA A+B+DR: all loci were analyzed together, 0–6 mm.

Patient survival

In their multicenter analysis of 10 752 heart transplants reported to the UNOS Scientific Registry, Hosenpud *et al.* [68] noted a progressive reduction in mortality risk at 3 years for increased HLA compatibility (1 or 2 matches: RR = 0.83; 3 matches: RR = 0.67; 4–6 matches: RR = 0.59; $P \leq 0.01$), primary benefit at HLA-A and -DR loci (RR = 0.87 and 0.79, respectively; $P < 0.001$). The small multicenter study by Valeri *et al.* [74] found that HLA-B and -DR matching had a positive effect on 1- and 3-year survival in 92 patients. One-year survival for heart transplants that shared two or more HLA-B or -DR antigens was 100% as compared to 87.5% for heart transplants that shared one or no HLA-B or -DR antigens. At 3 years, the corresponding figures were 100% and 50%, respectively. However, Mascaretti [16], Park [71], and Poli [20] collectively reported on 1165 heart transplant recipients in multicenter studies, without any significant correlation. Of the single-center studies, only a minority (4/10) found a significant effect of HLA mismatch on patient survival.

Effects of mismatch at the HLA-DR locus (0–1 vs. 2) on outcome, meta-analysis

Six studies provided data concerning graft survival at 1 year (Fig. 2a). All trials except one (Sheldon [60]) were favorable for less mismatch, with a pooled RR of 1.09 (95% CI: 1.01–1.19; $P = 0.04$). There was heterogeneity between study estimates ($I^2 = 63\%$). Restriction of the meta-analysis to studies that included heart transplantations performed until 1991 (four studies) reduced heterogeneity ($I^2 = 0\%$) and were still in favor of less mismatch with a pooled RR of 1.19 (95% CI: 1.09–1.30; $P < 0.0001$). Four studies reported data on patient survival at 1 year (Fig. 2b). Fewer mismatches at the HLA-DR locus did not lead to a significant increase in patient survival (pooled RR = 1.04; CI: 0.96–1.13; $P = 0.33$). Heterogeneity was low ($I^2 = 9\%$). Four studies that reported on graft rejection at 1 year were included in the analysis. Matching at the HLA-DR locus led to a significant reduction in the incidence of graft rejection with a pooled RR of 0.81 (CI: 0.66–0.99; $P = 0.04$) and with little heterogeneity ($I^2 = 31\%$; $P = 0.22$). Analysis of HLA-A or -B, or of HLA-A, -B, and -DR together, was not meaningful as there were three or less studies that shared a common outcome, follow-up, HLA antigen, and number of mismatches.

Publication bias

The funnel plots for graft survival, patient survival, and graft rejection showed adequate symmetry, suggesting minimal publication bias. However, the number of studies included was less than ten, making the funnel plots difficult to interpret.

Discussion

This systematic review and meta-analysis was performed to evaluate the importance of HLA matching in heart transplantation. To our knowledge, this is the first study of its kind in the field of heart transplantation. Most of the trial results support the conclusion that HLA matching increases graft survival and reduces the incidence of graft rejection. The benefit of HLA matching was especially prominent at the HLA-DR locus. Regarding patient survival and the incidence of CAV, the results have not been as unified. The present meta-analysis provided useful information on the protective effect of matching at the HLA-DR locus on prevention of graft failure. The pooled results from trials that compared 0–1 mismatches with 2 mismatches showed a statistically significant reduction in graft failure and graft rejection at 1 year. HLA-DR matching could improve graft survival by 9% and reduce the incidence of graft rejection by 19%. This should be balanced against the increased cost and logistical burden of HLA matching and the longer cold-ischemic times that may result from reliance on tissue typing.

To make HLA matching useful in terms of clinical feasibility, it has been suggested that the matching should be restricted to the HLA-DR locus [18]. Recipients who have organs with better HLA matching may require less immu-

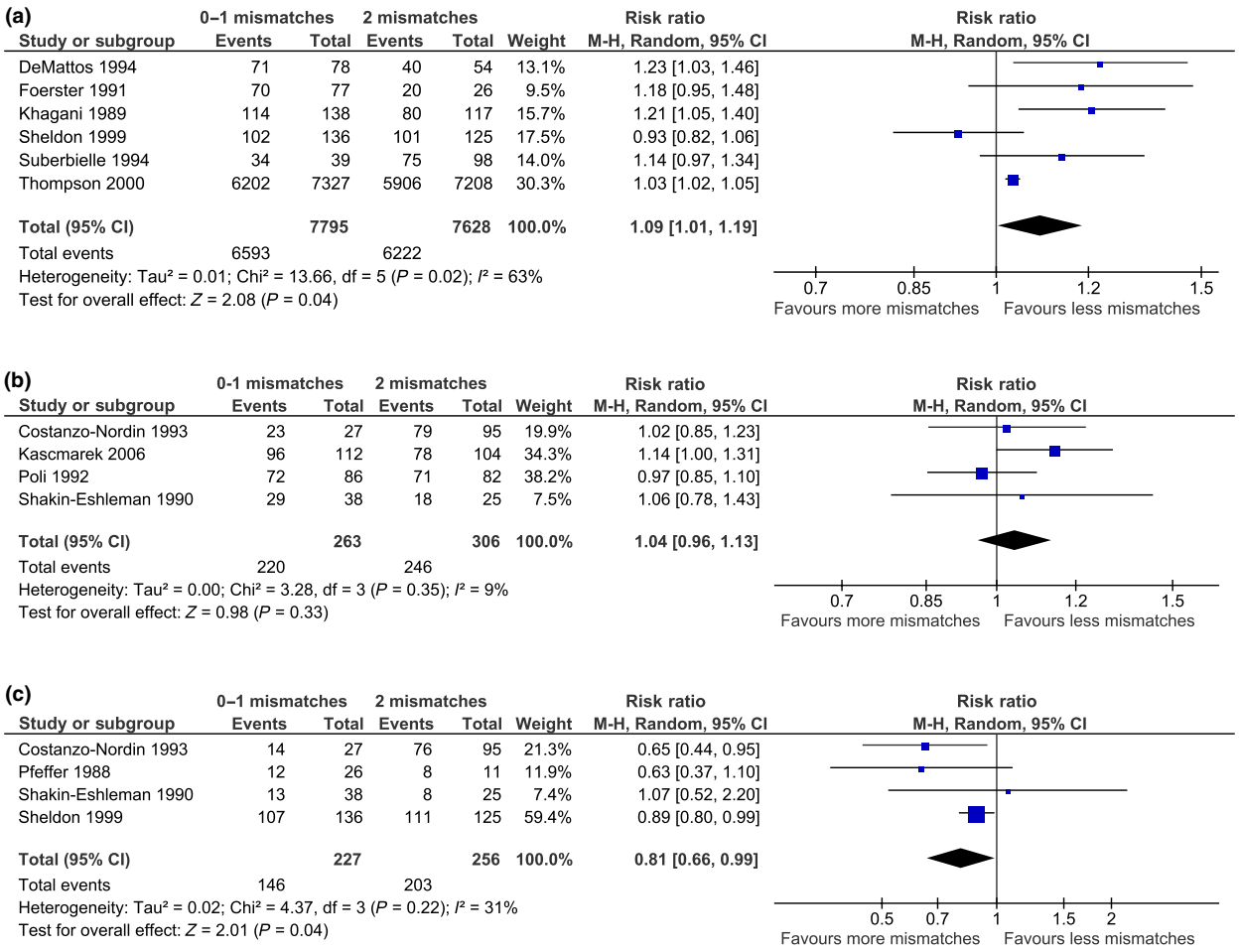

Figure 2 Forest plots showing influence of matching (0–1 vs. 2 human leukocyte antigen-DR mismatches) on outcome. (a) 1-year graft survival; (b) 1-year patient survival; (c) incidence of graft rejection at 1 year. Data across studies were pooled using random-effects model. Risk ratios are shown with 95% confidence intervals.

nosuppression, leading to a reduced rate of infections and malignancies—although a randomized trial would be needed to confirm or refute this [76]. In the case of heart transplantation, some patients require urgent transplant. Even though mechanical circulation support has been introduced, this situation has not changed much. In contrast to kidney transplantation, in heart transplantation, there is a shortage of critical donors and the current preservation techniques limit acceptable duration of ischemia (to <4 h) [65]. There is a correlation between longer duration of ischemia and poorer outcome after heart transplantation. Furthermore, matching of age, gender, and size have higher priority than HLA matching [77,78]. Today, DNA-based HLA typing has largely replaced the serological methods used previously. DNA-based HLA typing methods, utilizing sequencing-based typing (SBT) and the technologies of sequence-specific primers (SSP) and sequence-based oligonucleotides (SSO), are more precise than the serological methods used previously and provide results within hours, making it feasible in the clinical settings of a heart transplantation [79].

Human leukocyte antigen-A, -B, and -DR typing can be performed at low resolution by serology, detecting less than one hundred allelic specificities, or at high resolution (four-digit, genomic), detecting several hundred allelic specificities. It is possible that allelic disparities at the four-digit level could explain the conflicting results regarding outcome [80,81].

Because of the polymorphism of HLA, obtaining a complete HLA match just by chance is unlikely. According to Opelz *et al.*, the probability of achieving a complete match between a "random" donor and a recipient is less than 1.5%. However, in a pool of 1000 recipients, it was possible to find over 60% of donor–recipient pairs with two mis-

matches or less [19]. To determine whether prospective HLA matching is possible, DiSesa *et al.* [37] performed hypothetical matching by analyzing the HLA type of the recipients in their heart transplant list ($n = 47$) and in all potential heart donors in the geographic area east of the Mississippi River. When broad specificities were used, they found that 94% of the recipients on the list had at least one potential donor with at least four matches (of six). They concluded that prospective HLA matching is feasible.

Human leukocyte antigen match is one immunological factor to consider in heart transplantation, especially in sensitized recipients who have preformed antibodies to HLA antigens [82]. In recent years, new solid-phase techniques have been introduced to detect allele-specific anti-HLA antibodies. Today, enzyme-linked immunosorbent assay (ELISA) and flow cytometry (HLA antigen-coated beads, Luminex) for detection of donor-specific antibodies (DSA) are the most sensitive and routinely used laboratory methods for testing [83,84]. In general, the presence of donor-specific anti-HLA antibodies before and after transplantation has been found to be associated with higher rates of rejection and poor allograft survival in all organs examined [85–90]. Furthermore, it has been shown in heart transplantation that DSA against HLA class I was associated with decreased short-term survival [91]. In kidney transplantation, increasing HLA mismatch is associated with a higher degree of HLA sensitization and lower regraft survival [92].

The lack of randomized data was the greatest limitation of the present study, as systematic reviews of retrospective studies are known to be sensitive to confounding. Every systematic review is limited by the level, detail, and quality of the original reports. The lack of standardization in the studies for many of the variables considered, such as follow-up, outcome, and HLA mismatch, limited the number of reports that could be included in the meta-analysis. Where significant heterogeneity in the available trials is found, expressed as an I^2 value of more than 60%, the results should be interpreted with caution. We are well aware of introducing heterogeneity by combining studies from different centers in different geographic locations with different treatment protocols. Although information regarding exact dosage and treatment length was lacking for the most part, triple therapy with cyclosporine, azathioprine, and steroids was almost always stated. This is consistent with the studies being published in the 90s, before the addition of mycophenolate mofetil and tacrolimus to the treatment arsenal. It should also be noted that only one multicenter study and only three single-center studies have been published since 2000. With the improvements in other aspects of post-transplant care and therefore in survival with time, it is reasonable to expect that any absolute benefit from matching might be reduced in a modern cohort.

In conclusion, the available evidence suggests that HLA mismatch affects graft survival and graft rejection after heart transplantation. Thus, to obtain improved outcome after transplantation, HLA matching might be considered before surgery, especially for HLA-DR. The effects of HLA mismatch on patient survival and CAV are less clear, and they require further investigation. Randomized prospective studies are needed to settle these issues, given the practicality of HLA matching in heart transplantation in light of the new technology in high-resolution HLA typing.

Authorship

DA: study design, data collection, data analysis and writing of the article. DB: contributed to study design, data analysis, writing and reviewing the article. JN: study design, data acquisition, data collection, data analysis, writing and reviewing the article.

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