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The Effect of Genetic HLA Matching on Liver Transplantation Outcome

A Systematic Review and Meta-Analysis

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Objective: We aim to investigate the effects of genetically based HLA matching on patient and graft survival, and acute and chronic rejection after liver transplantation

Background: Liver transplantation is a common treatment for patients with end-stage liver disease. In contrast to most other solid organ transplantations, there is no conclusive evidence supporting human leukocyte antigen (HLA) matching for liver transplantations. With emerging alternatives such as transplantation of bankable (stem) cells, HLA matching becomes feasible, which may decrease the need for immunosuppressive therapy and improve transplantation outcomes.

Methods: We systematically searched the PubMed, Embase, and Cochrane databases and performed a meta-analysis investigating the effect of genetic HLA matching on liver transplantation outcomes (acute/chronic rejection, graft failure, and mortality).

Results: We included 14 studies with 2682 patients. HLA-C mismatching significantly increased the risk of acute rejection (full mismatching: risk ratio = 1.90, 95% confidence interval = 1.08 to 3.33, $P = 0.03$; partial mismatching: risk ratio = 1.33, 95% confidence interval = 1.07 to 1.66, $P = 0.01$). We did not discern any significant effect of HLA mismatching per locus on acute rejection for HLA-A, -B, -DR, and -DQ, nor on chronic rejection, graft failure, or mortality for HLA-DR, and -DQ.

Conclusions: We found evidence that genetic HLA-C matching reduces the risk of acute rejection after liver transplantation while matching for other loci does not reduce the risk of acute rejection, chronic rejection, graft failure, or mortality.

Keywords: acute rejection, HLA, HLA matching, human leukocyte antigen, liver transplantation, transplantation outcomes

INTRODUCTION

Despite improvement in short-term survival of liver transplantation recipients over the past decades,[1,2] long-term survival has remained suboptimal. With improved immunosuppressant therapies, the main cause of death after liver transplantation shifted from allograft rejection in 1987, to malignancies today. In addition to malignancies, long-term use of immunosuppressants is associated with infections, and renal, neurological, and liver dysfunction.[3–5] Strategies to reduce risks of allograft rejection and concomitant use of immunosuppression may contribute to improved transplantation outcomes.

Allograft rejection is categorized into 3 subtypes; hyperacute, acute, and chronic rejection. Hyperacute rejection, which is rare among ABO-compatible liver transplantations,[6] occurs during or immediately after transplantation. It results from the presence of preformed anti-donor antibodies that react to vascular endothelium and initiate coagulation and complement activation. Acute rejection develops in the first weeks to months after transplantation. It is characterized by a humoral and/or cellular immune response. The humoral immune response involves presence of donor-specific human leukocyte antigen (HLA) and non-HLA antibodies.[7,8] Sustained acute rejection can lead to tissue damage and is a major risk factor for chronic rejection, which occurs months to years after transplantation.[9,10] Chronic rejection is characterized by obliterative arteriopathy and destruction of biliary duct cells that lead to ductopenia in the liver graft.[11] Risk factors for chronic rejection are frequent and/or severe episodes of acute rejection, an elderly or unrelated donor, and the presence of donor-specific anti-HLA class I and II antibodies.[9,11]

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All available data are included in this publication.

S.A.F. and E.S. conceptualized the study. G.K. and E.F.I. performed the literature search, selection and performed all analyses. G.K. and E.F.I. wrote the article. R.H.J.H., C.A.L., E.E.S.N., and E.S. provided clinical insights and background information. G.K., E.F.I., E.E.S.N., E.S., and S.A.F. edited the final article.

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Thus, in both acute and chronic rejection, HLA complexes and alloreactive HLA antibodies play important roles.

HLA matching has improved outcomes for most solid organ transplantations,[12–18] but studies on liver transplantations have reported inconsistent results.[19–24] To date, most studies used serological HLA typing methods. Technological progress has enabled genetic typing of all HLA loci, which may reveal clinically relevant mismatches that were previously missed.[25] With emerging alternatives such as transplantation of bankable (stem) cells,[26–30] HLA matching becomes feasible, which may decrease the need for immunosuppressive therapy and improve transplantation outcomes. We therefore conducted a meta-analysis to investigate the effects of genetically based HLA matching on patient and graft survival, and acute and chronic rejection after liver transplantation.[31]

METHODS

We systematically searched the PubMed, Embase, and Cochrane databases (Fig. 1) up to February 15, 2022, for combinations of search terms: "liver transplant*/graft," "HLA/human leukocyte antigen," "(mis)match*/typing," and "outcome/rejection/survival/recurrence/graft failure." Duplicates were removed. Article titles and abstracts were screened for description of first liver transplantations with genetic HLA typing. Selected full-text articles were screened for eligibility based on the following inclusion criteria: first liver transplantation, genetic HLA typing, specified HLA locus mismatches in at least 1 locus, specified transplantation outcome with rejection type, patient mortality and/or graft failure, and association of number of HLA mismatches (0, 1 or 2) to outcomes. Exclusion criteria were: (additional) transplantations other than liver, unspecified HLA loci, re-transplantations, articles not available in English, and unavailable full texts (Table 1).

TABLE 1.

Inclusion and Exclusion Criteria

Inclusion	Exclusion
First liver transplantation	Transplantations other than liver in history, simultaneous, or during follow-up
Genetic HLA typing	Serological HLA typing
Specified HLA locus mismatches (at least 1)	Unspecified HLA loci
Specified transplantation outcome (rejection type, patient survival, graft failure)	Re-transplantations
Outcome association to HLA match (0, 1, and 2)	Article not in English
	Full-text not available

The quality of included studies was assessed using the Cochrane risk of bias assessment.[32] For the meta-analysis, studies describing all primary liver transplantation indications were combined and the effects of HLA matching on acute and chronic rejection, graft failure, and mortality were analyzed per locus (HLA-A, -B, -C, -DR, and -DQ). Risk ratios for these outcomes were determined for 0 versus 1, 1 versus 2, and 0 versus 2 mismatches per HLA locus. Findings of combined loci effects were included when available. Transplantations for autoimmune diseases were also analyzed separately to evaluate a putative favorable effect of mismatching to prevent autoimmune disease recurrence.

All analyses were performed using Cochrane's Review Manager version 5.4. Risk ratios were calculated using a random-effects model.[33] Associations between control and experimental conditions were tested with a Cochran-Mantel-Haenszel test. Overall test effects were estimated using Z-scores and *P*-values, with $\alpha = 0.05$.

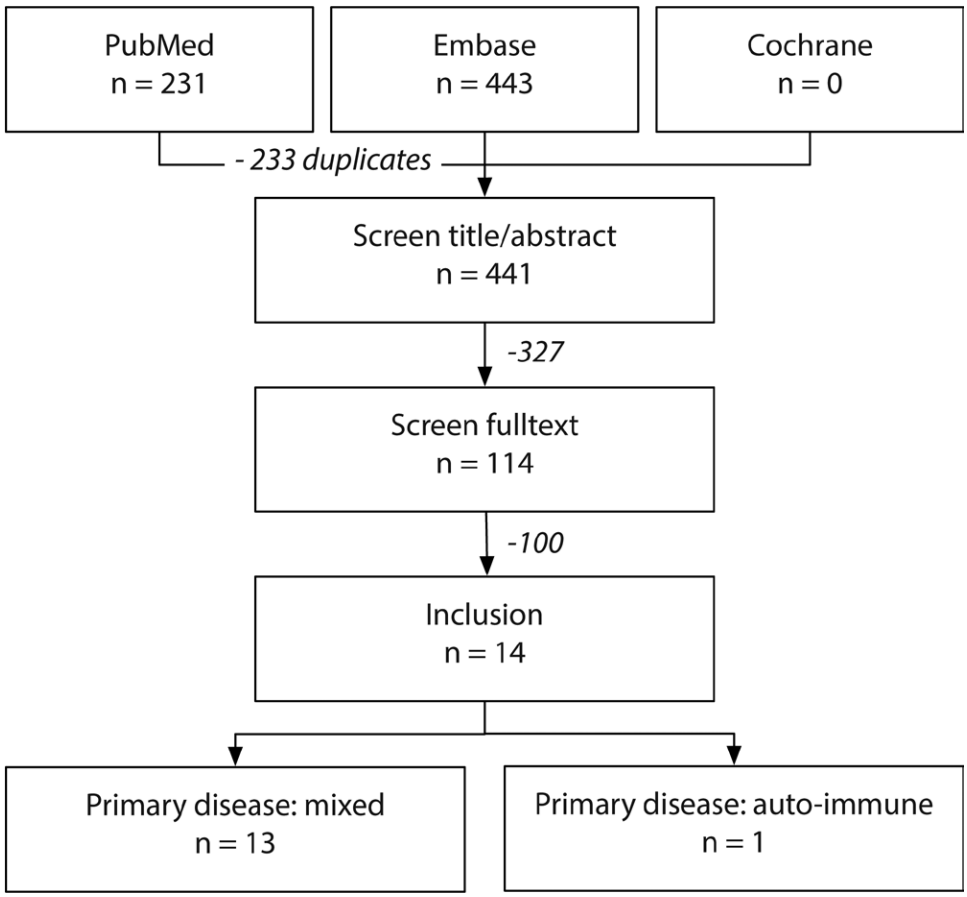

FIGURE 1. Flowchart of the systematic search and literature selection.

RESULTS

We identified 14 retrospective cohort studies that met the inclusion criteria. These articles were published between 1993 and 2021 and reported a total of 2682 transplantations (Fig. 1). 13 studies involved liver transplantations for different primary disease types, or did not specify transplantation indication, and 1 study evaluated liver transplantations for only autoimmune disease (Table 2 and Supplemental Table S1, http://links.lww.com/AOSO/A251). Immune suppressant regimens varied between studies (Supplemental Table S1, http://links.lww.com/AOSO/A251).

The effect of HLA matching on acute rejection

HLA Class I mismatching

To determine the effect of HLA mismatching on acute rejection, we examined the impact of genetic mismatches per class I locus (Table 3). Seven studies explored the effect of HLA-A matching in a total of 1073 patients with various transplantation indications. One study (n = 67) found that 2 HLA-A mismatches were more frequently associated with acute rejection. Thirteen (19.4%) patients developed acute rejection, 10 (76.9%) of which had 2 mismatches for locus HLA-A. All patients were preformed donor-specific antibody (DSA) naive before transplantation.[45] Another study (n = 45) found that 2 HLA-A mismatches significantly increased risk of acute rejection over 1 but not 0 HLA-A mismatches.[47] However, the number of patients with 1 mismatch was very small (n = 6).[47] The other studies did not find a significant association between HLA-A mismatching and acute rejection.[38,42–44,46] When combining all studies, HLA-A compatibility (partial/ full) did not significantly influence acute rejection (Fig. 2).

The same 7 studies also evaluated the effect of HLA-B matching on acute rejection. No significant associations were found between HLA-B mismatching and acute rejection,[38,42–47] individually nor when taken together (Fig. 2).

TABLE 2.

Characteristics of Included Articles

First Author[ref]	Year*	Type	Year of LTx	Country	Number of LTx†	HLA Loci	Outcome	Time of Follow-Up (Range)
Doran[34]	2000	RC	1986 to 1998	Australia	71	A, B	AR, graft survival in patients with autoimmune diseases	At least 1 year
Donaldson[35]	1993	RC	1984 to 1991	UK	466	DR, DQ	VBDS (CR), graft survival 1 year	At least 1 year
Francavilla[36]	1998	RC	1991 to 1996	England	135	DRB1, DQB1	AR, graft survival (1 and 5 years), patient survival (1 and 5 years)	At least 1 year
Poli[37]	1998	RC	1990 to 1997	Italy	517	DRB1	Graft survival 2 years	At least 2 years
Oertel[38]	2000	RC	NA	Germany	35	A, B, C, DR, DQ	AR	At least 1 year
Campos[39]	2003	RC	2000 to 2002	Spain	20	DRB1, DQB1	AR	3 to 30 months
Moya-Quiles[40]	2003	RC	1993 to 1999	Spain	100	C	AR	At least 5 years
Lopez-Alvarez[41]	2009	RC	NA	Spain	300	C	AR	At least 1 year
Muro[42]	2012	RC	1997 to 2005	Spain	224	A, B, DRB1, DQB1	AR, CR	At least 5 years
Legaz[43]	2013	RC	NA	Spain	402	A, B, C	AR	At least 1 year
Na[44]	2015	RC	2008 to 2013	Korea	270	A, B, DR	AR	Median 31 months (1–68)
Forner[45]	2018	RC	2009 to 2013	Canada	67	A, B, C, DRB1	AR	Mean 895 days (0-1,911)
Boix[46]	2020	RC	?	Spain	30	A, B, DRB1	AR	At least 1 year
Ono[47]	2021	RC	2010 to 2019	Japan	45	A, B, C, DRB1, DQB1	AR	Annual CFSE-MLR assays

*Year of publication.

†Number of LTx that were included in these analyses.

LTx indicates liver transplantation; NA, not available; VBDS, vanishing bile duct syndrome as symptom for CR (chronic rejection).

TABLE 3.

Results Meta-Analyses

Outcome	HLA	No. Studies	Events/Patients (%)			0 vs 1 MM		1 vs 2 MM		0 vs 2 MM	
			0 MM	1 MM	2 MM	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
	Acute rejection										
	A	7	29/144 (20.1%)	121/486 (24.9%)	133/443 (30.0%)	0.92 (0.64–1.33)	0.67	1.10 (0.80–1.51)	0.55	1.05 (0.68–1.62)	0.82
	B	7	10/63 (17.3%)	101/424 (25.1%)	172/587 (29.3%)	0.88 (0.44–1.74)	0.71	1.06 (0.85–1.32)	0.61	1.06 (0.52–2.61)	0.88
	C	6	10/60 (16.7%)	88/361 (24.4%)	176/528 (33.3%)	1.40 (0.79–2.49)	0.26	1.33 (1.07–1.66)	***0.01***	1.90 (1.08–3.33)	***0.03***
	DR	8	16/88 (18.2%)	117/381 (30.7%)	125/355 (35.2%)	0.93 (0.61–1.41)	0.73	0.99 (0.75–1.31)	0.96	0.98 (0.63–1.53)	0.93
	DQ	5	14/53 (26.4%)	96/235 (40.8%)	74/171 (41.8%)	1.07 (0.68–1.69)	0.77	1.06 (0.86–1.31)	0.59	1.17 (0.67–2.03)	0.56
	Chronic rejection										
	DR	2	1/14 (7.1%)	24/122 (19.7%)	23/162 (14.2%)	2.61 (0.56–12.13)	0.22	0.82 (0.40–1.69)	0.59	1.96 (0.42–9.26)	0.40
	DQ	2	13/43 (30.2%)	26/154 (16.9%)	11/121 (9.1%)	0.71 (0.39–1.29)	0.26	0.75 (0.29–1.91)	0.54	0.76 (0.35–1.66)	0.49
	Graft failure										
1-year	DR	2	26/62 (41.9%)	141/387 (36.4%)	103/340 (30.3%)	0.87 (0.63–1.20)	0.41	0.84 (0.69–1.04)	0.11	0.75 (0.54–1.06)	0.10
	DQ	1	3/8 (37.5%)	20/74 (27.0%)	13/53 (24.5%)	0.72 (0.27–1.90)	0.51	0.91 (0.50–1.66)	0.75	0.65 (0.24–1.80)	0.41
2-year	DR	1	14/50 (28.0%)	84/320 (26.3%)	76/321 (23.7%)	0.94 (0.58–1.52)	0.79	0.90 (0.69–1.18)	0.45	0.85 (0.52–1.37)	0.50
5-year	DR	1	0/1 (0.0%)	21/57 (36.8%)	19/77 (24.7%)	1.48 (0.13–16.74)	0.75	0.67 (0.40–1.12)	0.13	1.00 (0.09–11.37)	1.00
	DQ	1	4/8 (50.0%)	22/74 (29.7%)	14/53 (26.4%)	0.59 (0.27–1.29)	0.19	0.89 (0.50–1.57)	0.68	0.53 (0.23–1.21)	0.13
	Mortality										
1-year	DR	1	0/1 (0.0%)	8/57 (14.0%)	10/77 (13.0%)	0.59 (0.05–7.00)	0.67	0.93 (0.39–2.20)	0.86	0.54 (0.05–6.34)	0.62
	DQ	1	2/8 (25.0%)	8/74 (10.8%)	8/53 (15.1%)	0.43 (0.11–1.70)	0.23	1.40 (0.56–3.48)	0.47	0.60 (0.16–2.35)	0.47
5-year	DR	1	0/1 (0.0%)	13/57 (22.8%)	12/77 (15.6%)	0.93 (0.08–10.74)	0.95	0.68 (0.34–1.38)	0.29	0.64 (0.06–7.46)	0.72
	DQ	1	3/8 (37.5%)	12/74 (16.2%)	10/53 (18.9%)	0.43 (0.15–1.22)	0.11	1.16 (0.54–2.49)	0.70	0.50 (0.18–1.44)	0.20

Positive risk ratio (RR) indicates increased risk of outcome with increased mismatches.

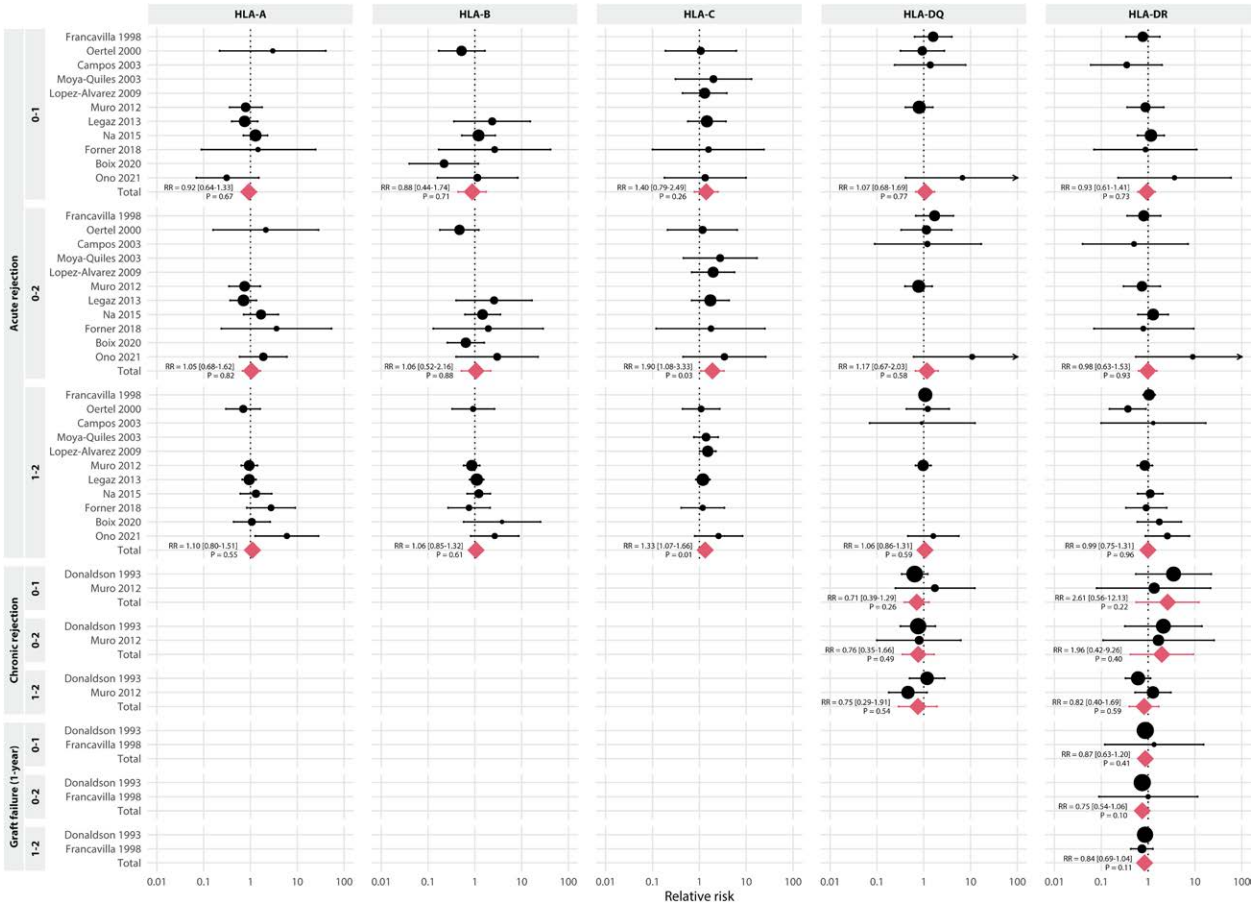

FIGURE 2. Forest plots of the effect of HLA-A, B, C, DR, and DQ mismatching on acute rejection, chronic rejection, and graft failure for patients with mixed primary diseases comparing 0 to 1, 1 to 2, and 0 to 2 mismatches. Positive risk ratio (RR) indicates increased risk of outcome with increased mismatches.

For HLA-C, 6 studies comprising a total of 949 patients showed that full mismatching compared to full matching significantly increased the risk of acute rejection (risk ratio [RR] = 1.90; 95% confidence interval [CI] = 1.08 to 3.33; $P = 0.03$), as did full versus partial mismatching for this locus (RR = 1.33; 95% CI = 1.07 to 1.66; $P = 0.01$, Fig. 2). One study found that patients with 2 HLA-C mismatches had a significantly higher rate of acute rejection (34.7%) than partially (23%) or totally (17.6%) matched patients (OR = 1.85; 95% CI = 3.12 to 1.10; $P = 0.02$). 84% of all acute rejection episodes happened within the first month after transplantation with a mean of 23.8 ± 4.9 days.[41] Similarly, another study found that higher HLA-C incompatibility increased the incidence of acute rejection (defined as <6 weeks after transplantation): 2 mismatches: 46.3%; 1 mismatch: 33.2%, 0 mismatches: 16.6%, although not significantly ($P = 0.12$).[40] Lastly, a study reported that specifically, recipient HLA-C genotype seemed to influence the risk of acute rejection.[43]

HLA Class II Mismatching

Of the 8 studies that reported the effect of HLA-DR mismatching on acute rejection in 824 patients, none found a significant effect.[36,38,39,42,44–47] One study found an association between HLA-DRB1*13 positive donors and acute rejection. Of the patients with acute rejection, 54% had a donor with this variant, compared to only 5% of patients without rejection ($P = 0.02$).[38] Overall, however, HLA-DR mismatching did not significantly influence acute rejection (Fig. 2).

Five studies (n = 459) assessed the effect of HLA-DQ matching on acute rejection. None of these studies found any association between HLA-DQ mismatching and acute rejection (Fig. 2).[36,38,39,42,47] However, 1 study (n = 135) found a significant increase in the need for high-dose steroids and tacrolimus in patients with 1 mismatch for HLA-DQ, compared with those without mismatches ($P < 0.03$), independent of the incidence or severity of acute rejection.[36]

The Effect of HLA Mismatching on Chronic Rejection of Liver Grafts, Graft Failure, and Mortality

We found no studies evaluating mismatching of HLA class I loci in relation to chronic rejection, graft failure, or mortality.

Two studies described the effect of HLA-DR (n = 298) and -DQ (n = 318) mismatching on chronic rejection (Fig. 2 and Table 3). In the first study (n = 95), 31 patients experienced chronic rejection (33%), characterized by vanishing bile duct syndrome (VBDS). There was no significant association between VBDS and HLA-DR or -DQ mismatching.[35] The other study included 224 patients who received cadaveric liver grafts of whom 20 (9%) developed chronic rejection, characterized by disappearing interlobular bile ducts with mononuclear portal infiltrates that later became fibrotic with enlarged portal tracts. They did not find an association between HLA-DR or -DQ mismatching and chronic rejection.[42] When taken together, HLA-DR and -DQ mismatching did not associate with chronic rejection (Fig. 2).

Two studies (n = 789) reported effects of HLA-DR mismatching on 1-year graft failure, and neither found an effect (Fig. 2 and Table 3). Causes of graft failure included chronic rejection, hepatitis, artery thrombosis, primary non-function, sepsis and recurrent cholangitis, Budd-Chiari syndrome, and primary biliary cirrhosis (PBC).[35,36]

One of the 2 studies (n = 135) also reported the effect of HLA-DR mismatching on 2- and 5-year graft survival, and the effect of HLA-DQ mismatching on 1- and 5-year graft survival.

No significant associations were found (Supplemental Figure S1, http://links.lww.com/AOSO/A250, and Table 3).[36] The same study further reported 1- and 5-year mortality in relation to HLA-DR and -DQ mismatching. 1- and 5-year mortality rates were 13% and 19%, respectively,[36] and no significant associations with HLA-subtype were found (Supplemental Figure S1, http://links.lww.com/AOSO/A250, and Table 3).

The Effect of HLA Mismatching for Patients With Autoimmune Diseases

Finally, we examined the role of HLA-A and -B matching in graft failure for patients with autoimmune diseases. A single study reported 63 patients with autoimmune chronic active hepatitis and primary biliary cholangitis, and 287 non-autoimmune diseases. They excluded primary sclerosing cholangitis from all analyses.[34] For patients with autoimmune disease, 1-year graft survival seemed to improve with more mismatches, although this was not statistically significant. Conversely, graft survival of patients without autoimmune disease decreased with more HLA-A or -B mismatches, with a reported statistical significance for HLA-B (0-1 mismatch: 82.8% survival rate; 2 mismatches: 75.0% ($P < 0.01$)). Unfortunately, we could not confirm this nor include their data in our meta-analysis because of the format of their data on acute rejection.

DISCUSSION

Although immune suppressive therapy after liver transplantation has undeniably improved short-term outcomes after liver transplantation, it is a major cause of current long-term complications. Improved insight in the role of HLA mismatching may improve liver transplantation outcomes. With our meta-analysis of 14 independent studies comprising a total of 2,682 patients, we found a significant effect of HLA-C mismatching on the incidence of acute rejection, both for 1 versus 2 mismatches (RR = 1.33; 95% CI = 1.07 to 1.66; $P = 0.01$) and 0 versus 2 mismatches (RR = 1.90; 95% CI = 1.08 to 3.33; $P = 0.03$). Conversely, we did not discern any significant effect of HLA mismatching per locus on acute rejection for HLA-A, -B, -DR, and -DQ, nor on chronic rejection, graft failure, or mortality for HLA-DR, and -DQ. Associations between mismatching of HLA-DR and 2- and 5-year graft failure, and HLA-DQ and 1-, 2-, and 5-year graft failure could not be meta-analyzed because data were derived from a single study (Supplemental Figure 1, http://links.lww.com/AOSO/A250). The possibility exists that we failed to detect existing associations due to the limited reported patient numbers using genetic HLA typing. Also, because of the study design and limited data availability, we were unable to consider immune suppression, which varied between patients and studies and evolved over the course of time. It is known that in some patients stopping immune suppression after liver transplantation is tolerated, while in others, this results in rejection.[48] Relating HLA matching in these subgroups to these outcomes would be highly insightful, but was impossible due to insufficient cases in our cohort.

Five of the 14 included articles in our meta-analysis carried a potential risk of bias (Fig. 3). Campos *et al.* (2003) failed to mention the statistic methodology.[39] Furthermore, Campos *et al.* (2003), Forner *et al.* (2018), Oertel *et al.* (2000), and Ono *et al.* (2021)[47] did not report the primary transplantation indication (attrition bias).[38,39,45] Donaldson *et al.* (1993) selected a subgroup of patients to genetically type HLA-DR for analysis of the effect of matching on VBDS, without providing a reason for this subgroup selection (attrition bias).[35] Forner *et al.* (2018) failed to accurately report time to rejection (detection bias).[45] Since the data from these studies with a potential risk of bias were usable for our research question, we included them in our analyses. Nevertheless, these studies should be interpreted with more caution. We excluded acute rejection data from Doran *et al.* (2000) because it was unclear whether biopsy scores were from all patients or from only those with acute rejection.[34]

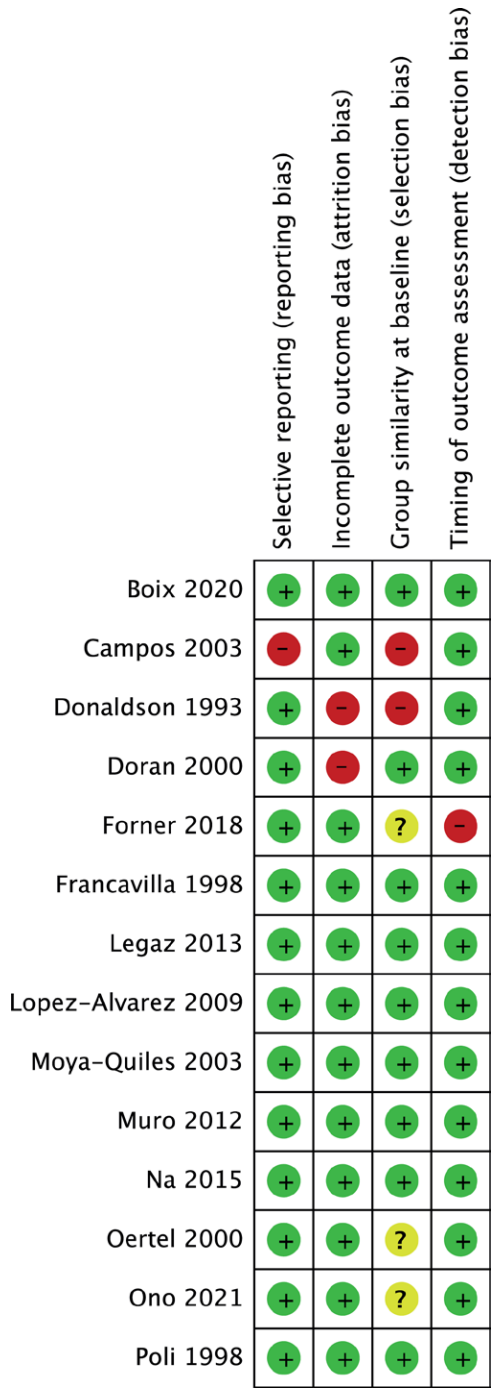

FIGURE 3. Cochrane risk of bias summary for all included studies.

Whether HLA matching for liver transplantation improves outcomes has long been a topic of debate. The most recent meta-analysis (2010) included 16 articles including serological, not DNA-based HLA typing.[31] The main finding was that combined HLA-A, -B, and -DR matching significantly decreased the incidence of acute rejection (0-2 vs 3-6 mismatches; n = 1268; RR = 0.77; 95% CI = 0.61 to 0.97; $P = 0.03$). Similar combined data were not available for meta-analysis from the articles included in the current study. Unfortunately, the previous meta-analysis did not provide data on HLA-C mismatching, the only locus we found to be associated with acute rejection

(Fig. 2). HLA-C eplet mismatching has previously been associated with acute rejection.[49] This may be explained by the interaction of HLA-C with killer immunoglobulin receptors expressed on NK cells and subsets of T-cells. Several other studies suggest that the HLA-C allelic subtype and killer immunoglobulin receptor subtype may interplay to either protect or activate immune responses.[41,43,50]

Not every mismatch has similar consequences. This has stimulated the development of new epitope-based matching algorithms. These algorithms use small polymorphisms on the outer domains of HLA molecules to calculate a mismatch score. For example, based on the B-cell-mediated immune response, the B-cell epitope discriminating HLAMatchmaker[51] is widely used and has been shown to correlate with graft outcome in various solid organ transplantations.[52] In addition, T cell-mediated alloreactivity is involved in allograft rejection after solid organ transplantation. T-cells recognize allogeneic HLA molecules on the surface of allogeneic cells in the direct pathway, and recognize mismatched HLA-derived epitopes that are presented by nonallogeneic cells in the indirect pathway. PIRCHE (Predicted Indirectly Recognizable HLA Epitopes) uses these T-cell epitopes to predict the likelihood of HLA-derived peptides to bind to HLA class-II molecules,[53] and matching using this algorithm has been shown to reduce formation of dnDSAs after kidney transplantation.[37] A recent study shows that PIRCHE-II mismatching may improve outcomes for young patients transplanted for autoimmune diseases.[52] On the other hand, the use of such algorithms may censor the effect of mismatching of a single-locus (e.g., HLA-C). Conversely, our study relying on aggregation of reported cases in literature made it impossible to study the effects of combined HLA locus (mis)matching on transplantation outcomes.

In conclusion, we found evidence that genetic HLA-C matching reduces the risk of acute rejection after liver transplantation. Novel techniques to evaluate HLA mismatch-derived peptides may further help to unravel this longstanding liver transplantation paradigm. This is particularly important with the emergence of novel bankable liver cell sources for transplantation, which enable precise matching for clinical practice.

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