World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i27.3457

World J Gastroenterol 2010 July 21; 16(27): 3457-3464
ISSN 1007-9327 (print)

BRIEF ARTICLE

Impact of human leukocyte antigen mismatching on outcomes of liver transplantation: A meta-analysis

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Received: January 4, 2010 Revised: February 20, 2010

Accepted: February 27, 2010

Published online: July 21, 2010

Abstract

AIM: To assess the effect of human leukocyte antigen (HLA) mismatching on liver graft outcome and acute rejection from a meta-analysis of available cohort studies.

METHODS: Articles in PubMed/MEDLINE, EMBASE and the Cochrane database from January 1970 to June 2009, including non-English literature identified in these databases, were searched. Only studies comparing HLA or sub-phenotype matching with mismatching were extracted. The percentage of graft survival was extracted by "Engauge Digitizer" from survival curves if the raw data were not displayed. A meta-analysis was performed when at least 3 studies provided data.

RESULTS: Sixteen studies met the inclusion criteria. A lower number of HLA mismatches (0-2 *vs* 3-6) did reduce the incidence of acute rejection (relative risk: 0.77, $P = 0.03$). The degree of HLA mismatching (0-2 *vs* 3-6) had no significant effect on 1-year [hazard ratio (HR): 1.04, $P = 0.68$] and 5-year (HR: 1.09, $P = 0.38$) graft survival. In sub-phenotype analysis, the degree of HLA-A, B and DR mismatching (0 *vs* 1-2) had no significant effect on 1-year and 5-year graft survival, either. The HRs and *P*-values were 0.95, 0.71 (HLA-A, 1-year); 1.06, 0.60 (HLA-A, 5-year); 0.77, 0.16 (HLA-B, 1-year); 1.07, 0.56 (HLA-DR, 1-year); 1.18, 0.23 (HLA-DR, 5-year), respectively.

CONCLUSION: The results of this systematic review imply that good HLA compatibility can reduce the incidence of acute rejection in spite of having no influence on graft outcomes. To obtain a short recovery time and minimize rejection post transplantation, HLA matching studies should be considered before the operation.

Key words: Human leukocyte antigen; Mismatching; Liver transplantation; Meta-analysis; Graft rejection

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Lan X, Zhang MM, Pu CL, Guo CB, Kang Q, Li YC, Dai XK, Deng YH, Xiong Q, Ren ZM. Impact of human leukocyte antigen mismatching on outcomes of liver transplantation: A meta-analysis. *World J Gastroenterol* 2010; 16(27): 3457-3464 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i27/3457.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i27.3457

INTRODUCTION

In the past 2 decades, deaths and other complications of organ transplantation have decreased significantly as a re-

sult of improvements in anesthesiology and surgical techniques. In addition, development of immunosuppressive agents and new organ preservation solutions have been shown to play a role in the improved survival rate. However, acute or chronic rejection remains the most important reason of graft failure, especially for patients who suffer from mismatching of human leukocyte antigen (HLA).

The role of HLA matching between donor and recipient in organ transplant rejection and survival has been widely studied and proven to increase graft survival after kidney, heart, and other organ transplantation and to reduce the incidence of acute or chronic rejection[1-6]. In contrast, major histocompatibility complex analysis is not routinely performed in liver transplantation because its importance remains controversial, with different groups reporting disparate results. It was reported that some populations of patients gained benefit from high degrees of HLA matching[7-14]. Concern has been voiced about possible increased likelihood of recurrence of primary disease with good HLA compatibility[15-25].

We therefore performed a systematic review and meta-analysis on the efficacy of HLA mismatching in all published controlled clinical trials on the outcomes of liver transplantation.

MATERIALS AND METHODS

Search strategy

Relevant articles that were published between January 1970 and June 2009 in PubMed/MEDLINE, EMBASE and the Cochrane database, including the non-English literature were identified. The search strategy used the following single text words and combinations: living donor liver transplantation (LDLT), liver transplantation (LT), orthotopic liver transplantation (OLT), human leukocyte antigen (HLA), major histocompatibility complex (MHC), histocompatibility, matching and mismatching. Reference lists of relevant articles were cross checked for other potentially relevant articles.

Selection of trials and quality of the studies

Three separate authors (Lan X, Pu CL and Guo CB) independently reviewed and evaluated all articles for inclusion, which were classified as randomized control trial (RCT), controlled trial (CT), or descriptive study. After the initial article selection, the article dataset was reviewed and updated to capture any articles published between the final consensus review and the final data analysis (Zhang MM). Only cohort studies were indentified because of a lack of RCT.

The scoring system was adapted from Stahl, the Cochrane Collaboration and others[26-29]. This system suits not only RCT but CT or other studies well: (1) Was the trial design clearly stated? (2) Selection bias questions: Was the Patient selection process clearly stated? If the trial was an RCT, were patients randomly allocated to the therapeutic intervention? Were patients and clinicians blinded to the intervention? If the trial was not an RCT, were confounders controlled for? If the trial design was case control were matching procedures clearly described and implemented? Were patient recruitment procedures clearly described? Were the intervention and control groups selected similarly? (3) Performance bias questions: Was the intervention clearly described? Was intervention clearly measured? (4) Attrition bias questions: Were patients followed up? Were they followed up for 2 or more explicitly defined intervals? If patients were lost/dropped out other than because of death, were they accounted for? Were all outcome measures captured at the declared follow-up intervals? (5) Detection bias questions: Were the outcome measures clearly described? Was measurement of the outcome measures blinded? (6) Were appropriate statistical methods used? Were *P*-values clearly stated? Was life table analysis provided, *etc*.; and (7) Was the presentation of data adequate, for example, in the article were endpoints clearly defined i.e. graft survival, patient survival, duration of follow-up, re-transplantation rate, *etc*.? Were survival curves provided or were sufficient data to construct survival curves provided, were donor and recipient variables clearly defined and presented?

These questions were placed on a 3 point scale: unclear/inadequate (0), adequate (1), good (2). Articles were considered for inclusion if their summary score exceeded 30.

Data extraction

Graft loss was measured by hazard ratio (HR) and rejection was measured by relative risk (RR) at 1-year and 5-year in every study by 2 independent reviewers, reconciling any differences by consensus or when in doubt referring it to a third reviewer (Zhang MM) for arbitration. Graft survival rate was extracted for calculating corresponding HR using the formula recommended by Parmar *et al*[30]. Data was extracted by the software "Engauge 4.0" from survival curves if it was not shown in articles directly. Donor/recipient HLA compatibility for HLA class Ⅰ (A and B), and HLA class Ⅱ (DR) was measured as the number of mismatches, locus-specific (0 to 2 mismatches) and overall for the A, B, and DR loci (0 to 6 mismatches).

Meta-analysis

Both HR and RR were compared between 0 with 1-2 mismatches for each locus (mismatches of the HLA-A, B and C loci respectively) and 0-2 with 3-6 mismatches for overall HLA-A, B and DR loci. Comparability of the studies included in each pooled analysis was confirmed by examination of the $\chi^2 Q$ (expressed as a *P*-value) and I^2 statistics of heterogeneity. Statistical heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$. Lack of over-influence of one individual study to pooled estimates was confirmed by serial omission of each study and examination of the resulting estimate. To account for potential differences that were evident clinically but not identified by statistical tests, random effects models were used for each outcome measure. All statistical analyses were performed using Review Manager 5.0 which was a new program for determining HR.

Table 1 Contents of included studies

Author	Location	Immunosuppression	Number of patients	Contents
Meyer *et al*[9]	France	Cyclosporine, methylprednisolone and azathioprine	162	HLA-A, B and DR (5-yr graft survival); HLA-DR (1- and 5-yr graft survival)
Jakab *et al*[10]	American	NS	631	HLA-A, B and DR (1- and 5-yr graft survival); HLA-A and HLA-B (5-yr graft survival)
Neumanna *et al*[8]	Germany	Cyclosporine, azathioprine and prednisolone	836	HLA-A, B and DR (1- and 5-yr graft survival and rejection); HLA-A and HLA-DR (1- and 5-yr graft survival); HLA-B (1-yr graft survival)
Hashimoto *et al*[11]	Japan	Cyclosporine, methylprednisolone and azathioprine	50	HLA-A, B and DR (1- and 5-yr graft survival)
Langrehr *et al*[12]	Germany	Cyclosporine, azathioprine and prednisolone	165	HLA-A, B and DR (1- and 5-yr graft survival and rejection)
Suehiro *et al*[13]	Japan	Tacrolimus and Steroids	104	HLA-A, B and DR (1- and 5-yr graft survival and rejection)
Harihara *et al*[14]	Japan	Tacrolimus and Steroids	85	HLA-A, B and DR (rejection)
Balan *et al*[7]	American	Cyclosporine, prednisone, and azathioprine or tacrolimus	799	HLA-A, B and DR (1- and 5-yr graft survival); HLA-A (5-yr graft survival)
Sugawara *et al*[16]	Japan	Tacrolimus and methylprednisolone	113	HLA-DR (1-yr graft survival)
Doran *et al*[22]	Germany	NS	446	HLA-A, B and DR (1- yr graft survival); HLA-A and HLA-B (1-yr graft survival)
Poli *et al*[15]	Italy	Cyclosporine, azathioprine and tacrolimus	814	HLA-DR (5-yr graft survival)
Yagihashi *et al*[18]	American	Cyclosporine, azathioprine and tacrolimus	347	HLA-A, HLA-B and HLA-DR (1-yr graft survival)
Nikaein *et al*[21]	American	Cyclosporine and prednisone	701	HLA-A, B and DR (1-yr graft survival); HLA-A (1- and 5-yr graft survival); HLA-B and HLA-DR (1-yr graft survival)
Markus *et al*[20]	American	NS	527	HLA-A (5-yr graft survival); HLA-DR (1-yr graft survival)
Donaldson *et al*[19]	Britain	Cyclosporine, azathioprine	466	HLA-A, B and DR (1-yr graft survival and rejection); HLA-A and HLA-B (1-yr graft survival)
Knechtle *et al*[17]	American	NS	324	HLA-A, B and DR (1-yr graft survival); HLA-A, HLA-B and HLA-DR (1-yr graft survival)

NS: Not specified; HLA: Human leukocyte antigen.

RESULTS

Results of the article selection are described in Figure 1. 1568 potentially relevant articles were identified in the search. The abstracts of these studies were reviewed by 2 independent investigators. One thousand four hundred and forty-two did not meet inclusion criteria as their summary score was less than 30. Publications eligible for analysis included 16 articles: 2 prospective studies[7,8] and 14 retrospective cohort studies[9-22]. Non RCTs were included in our studies. In 4 studies acute rejection rates were compared clearly between 0-2 mismatches and 3-6 mismatches of HLA[8,12-14]. That is too say, specific data could only be extracted in these 4 articles. In 10 and 8 studies 1-year and 5-year survival rates, respectively, were compared between 0-2 mismatches and 3-6 mismatches of HLA[7-10,12,13,15,17,19,21,22]. In 6 and 5 studies 1-year and 5-year survival rates, respectively, were compared or could be extracted from survival curves between 0 mismatches and 1-2 mismatches of the HLA-A epitope[7,8,10,17-22]. In 9 and 5 studies 1-year and 5-year survival rates, respectively, were compared or could be extracted from survival curves between 0 mismatches and 1-2 mismatches of the HLA-DR epitope[8,9,16-22]. In 6 studies 1-year survival rates were compared between 0 mismatches and 1-2 mismatches of the HLA-B epitope[8,17-19,21,22]. Although 0 mismatches of the HLA-B epitope were compared with 1-2 mismatches in 5-year survival rates in 3 articles, the statistical heterogeneity was $P = 0.004$ and $I^2 = 82\%$ in the meta-analysis. Hence, the HR of the HLA-B epitope in 5-year survival rates was not included in our discussion. Details of these studies are described in Table 1.

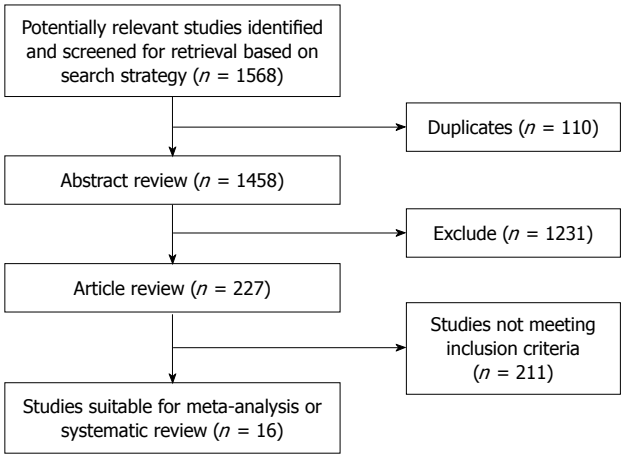


Figure 1 Selection of articles.

Table 2 Methodological quality of the controlled trials

Study	Selection criteria specified	Study design	Score	Other causing of death report	Dropouts explained	Funding
Meyer C	Yes	RCS	30	No	No	NS
Jakab SS	Yes	RCS	32	Yes	Yes	NS
Neumanna UP	Yes	PCS	31	No	No	NS
Morioka D	Yes	RCS	30	No	No	NS
Langrehr JM	Yes	RCS	33	Yes	Yes	NS
Suehiro T	Yes	RCS	30	Yes	No	NS
Harihara Y	Yes	RCS	30	No	No	NS
Vijayan B	Yes	PCS	35	Yes	Yes	NS
Sugawara Y	Yes	RCS	30	Yes	No	NS
Doran	Yes	RCS	30	No	No	NS
Poli F	Yes	RCS	31	No	No	NS
Yagihashi A	Yes	RCS	30	No	No	NS
Afzal N	Yes	RCS	33	No	No	NS
Markus BH	Yes	RCS	32	No	Yes	NS
Donaldson P	Yes	RCS	32	No	Yes	NS
Knechtle SJ	Yes	RCS	31	No	Yes	NS

RCS: Retrospective cohort studies; NS: Not specified.

The methodological quality of the studies was assessed using a validated tool as described above (Table 2).

Meta-analysis of HLA epitope

HLA-A, B and DR (0-2 mismatches *vs* 3-6 mismatches): In the studies included in the meta-analysis, a total of 4260 patients were included in 10 articles (1-year graft survival) and 3180 patients were included in 8 articles (5-year graft survival). No differences between 0-2 mismatches and 3-6 mismatches of HLA-A, B, and DR epitopes were seen in terms of 1-year graft survival [HR: 1.04, 95% confidence interval (CI): 0.86-1.25, $P = 0.68$] and 5-year graft survival (HR: 1.09, 95% CI: 0.90-1.32, $P = 0.38$, Figure 2).

HLA-A epitopes (0 mismatch *vs* 1-2 mismatches): Of the studies included in the meta-analysis, there were a total of 2049 patients in 6 articles (1-year graft survival) and 2138 patients in 5 articles (5-year graft survival). No differences between 0 mismatch and 1-2 mismatches of the HLA-A epitopes were seen in terms of 1-year graft survival (HR: 0.95, 95% CI: 0.72-1.25, $P = 0.71$) and 5-year graft survival (HR: 1.06, 95% CI: 0.85-1.34, $P = 0.60$, Figure 2).

HLA-B epitopes (0 mismatch *vs* 1-2 mismatches): A total of 1969 patients were included in 6 articles (1-year graft survival). No differences between 0 mismatch and 1-2 mismatches of the HLA-B epitopes were seen in terms of 1-year graft survival (HR: 0.77, 95% CI: 0.53-1.11, $P = 0.16$, Figure 2).

HLA-DR epitopes (0 mismatch *vs* 1-2 mismatches): A total of 2688 patients were included in 9 articles (1-year graft survival) and 2175 patients were included in 5 articles (5-year graft survival). No differences between 0 mismatch and 1-2 mismatches of the HLA-DR epitopes were seen in terms of 1-year graft survival (HR: 1.07, 95% CI: 0.84-1.37, $P = 0.56$) and 5-year graft survival (HR: 1.18, 95% CI: 0.90-1.54, $P = 0.23$, Figure 2).

HLA epitopes and acute rejection

A total of 1268 patients were included in 4 articles (acute rejection within 3 mo after transplantation). Significant differences between 0-2 mismatches and 3-6 mismatches of HLA-A, B and DR epitopes were seen in terms of acute rejection (RR: 0.77, 95% CI: 0.61-0.97, $P = 0.03$, Figure 2).

DISCUSSION

This is the first systematic review and meta-analysis on the effect of HLA mismatching in short and long term liver graft outcome and acute rejection. We identified and analyzed 16 unique cohort studies and all HLA locus-specific analyses were performed by standard lymphocytotoxicity tests with confirmation by polymerase chain reaction, with HLA-A, B and DR locus mismatches being compared. The results clearly showed that a lower number of HLA mismatches (0-2 *vs* 3-6) did reduce the incidence of acute rejection. The degree of HLA mismatching (0-2 *vs* 3-6) had no significant effect on 1-year and 5-year graft survival. Furthermore, we found no difference between 0 mismatches and 1-2 mismatches in 1-year and 5-year graft survival of HLA-A, HLA-B and HLA-DR on subgroup analysis.

The role of HLA matching between donor and recipient in liver transplant rejection and graft survival has been determined in some cohort studies and there still is no consensus view[7-15,31]. This systematic review analyzed the different data of various studies and has given our own results. However, the main objective in performing this analysis was to assess the necessity of donor-recipient HLA matching before liver transplantation.

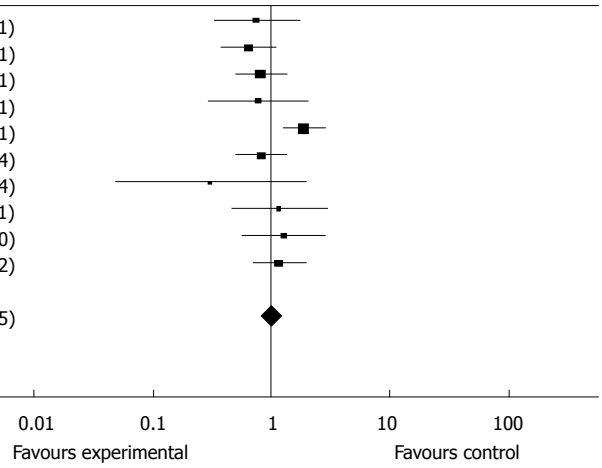
As the role of HLA matching between donor and recipient in organ transplant rejection and survival had been proven to increase graft survival after kidney and heart transplantation, it has been debated whether these matches affected the outcomes of the liver graft similarly. In liver transplantation, organ allocation relies mostly on ABO blood group, recipients' body weight, and clinical urgency, and the outcome of liver grafts relies mostly on complications after transplantation; HLA matching is usually not taken into account and the literature is inconsistent on the role of this parameter. In fact, any complications after transplantation are associated with graft outcome and rejection. Liver artery thrombosis, venous thromboembolic complications, seventh-day syndrome, primary graft nonfunction, and serious infection can decrease survival[32-36]. Compared to HLA mismatching, these complication are more important for long term graft survival.

Although the liver graft was considered to be a kind of immune-free organ, in our meta-analysis a lower number of HLA mismatches (0-2 *vs* 3-6) did reduce the incidence of acute rejection. It has become clear in recent years that mismatching of HLA in liver grafts led to endothelialitis induced by the recipient's natural killer cells and so rejection was instigated. The association of acute rejection with

A

Study or subgroup	Weight (%)	Hazard ratio Exp [(O-E)/V], fixed, 95% CI
Nikaein A 1994	5.3	0.76 (0.34, 1.71)
Morioka D 2007	12.0	0.65 (0.38, 1.11)
Doran TJ 2000	16.2	0.83 (0.52, 1.31)
Langrehr JM 2006	3.9	0.78 (0.30, 2.01)
Donaldson P 1993	22.5	1.90 (1.28, 2.81)
Jakab SS 2007	15.3	0.83 (0.52, 1.34)
Knechtle SJ 1993	1.0	0.31 (0.05, 1.94)
Suehiro T 2005	4.1	1.17 (0.47, 2.91)
Neumann UP 2002	5.6	1.27 (0.58, 2.80)
Balan V 2008	14.1	1.17 (0.72, 1.92)
Total (95% CI)	100.0	1.04 (0.86, 1.25)

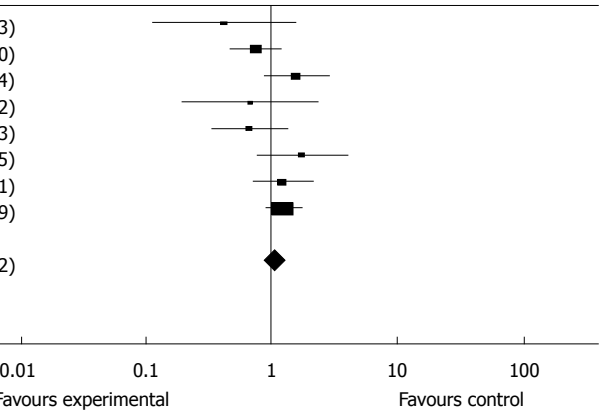
Heterogeneity: χ^2 = 16.95, *df* = 9 (*P* = 0.11); I^2= 47%
Test for overall effect *Z* = 0.42 (*P* = 0.68)



B

Study or subgroup	Weight (%)	Hazard ratio Exp [(O-E)/V], fixed, 95% CI
Meyer C 1997	2.2	0.42 (0.12, 1.53)
Morioka D 2007	17.6	0.76 (0.48, 1.20)
Poli F 2001	10.7	1.57 (0.87, 2.84)
Langrehr JM 2006	2.4	0.67 (0.19, 2.32)
Jakab SS 2007	8.0	0.67 (0.34, 1.33)
Suehiro T 2005	5.7	1.76 (0.78, 3.95)
Neumann UP 2002	13.2	1.24 (0.73, 2.11)
Balan V 2008	40.1	1.25 (0.92, 1.69)
Total (95% CI)	100.0	1.09 (0.09, 1.32)

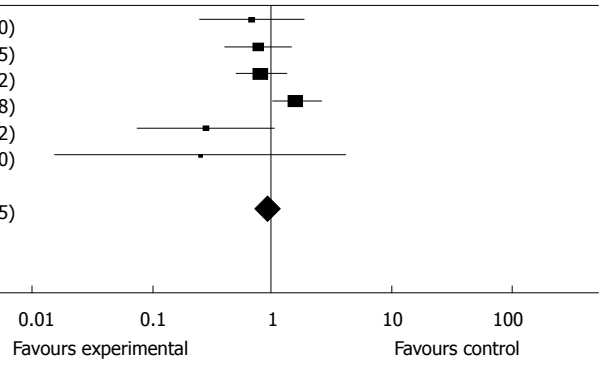
Heterogeneity: χ^2 = 10.77, *df* = 7 (*P* = 0.15); I^2= 35%
Test for overall effect *Z* = 0.88 (*P* = 0.38)



C

Study or subgroup	Weight (%)	Hazard ratio Exp [(O-E)/V], fixed, 95% CI
Yagihashi A 1992	7.5	0.70 (0.26, 1.90)
Nlkaeln A 1994	19.6	0.78 (0.42, 1.45)
Jakab SS2007	33.3	0.82 (0.51, 1.32)
Donaldson P 1993	33.9	1.61 (1.00, 2.58)
Knechtle SJ 1993	4.6	0.29 (0.08, 1.02)
Neumann UP 2002	1.0	0.26 (0.02, 4.10)
Total (95% CI)	100.0	0.95 (0.72, 1.25)

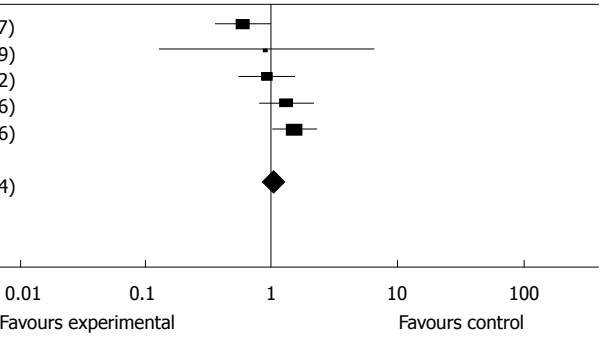
Heterogeneity: χ^2 = 10.18, *df* = 5 (*P* = 0.10); I^2= 49%
Test for overall effect *Z* = 0.37 (*P* = 0.71)



D

Study or subgroup	Weight (%)	Hazard ratio Exp [(O-E)/V], fixed, 95% CI
Balan V 2008	22.9	0.60 (0.37, 0.97)
Neumann UP 2002	1.4	0.91 (0.13, 6.49)
Jakab SS 2007	21.1	0.93 (0.56, 1.52)
Markus BH 1988	21.8	1.32 (0.81, 2.16)
Nikaein A 1994	32.9	1.52 (1.02, 2.26)
Total (95% CI)	100.0	1.06 (0.85, 1.34)

Heterogeneity: χ^2 = 5.13, *df* = 3 (*P* = 0.16); I^2= 42%
Test for overall effect *Z* = 0.53 (*P* = 0.60)



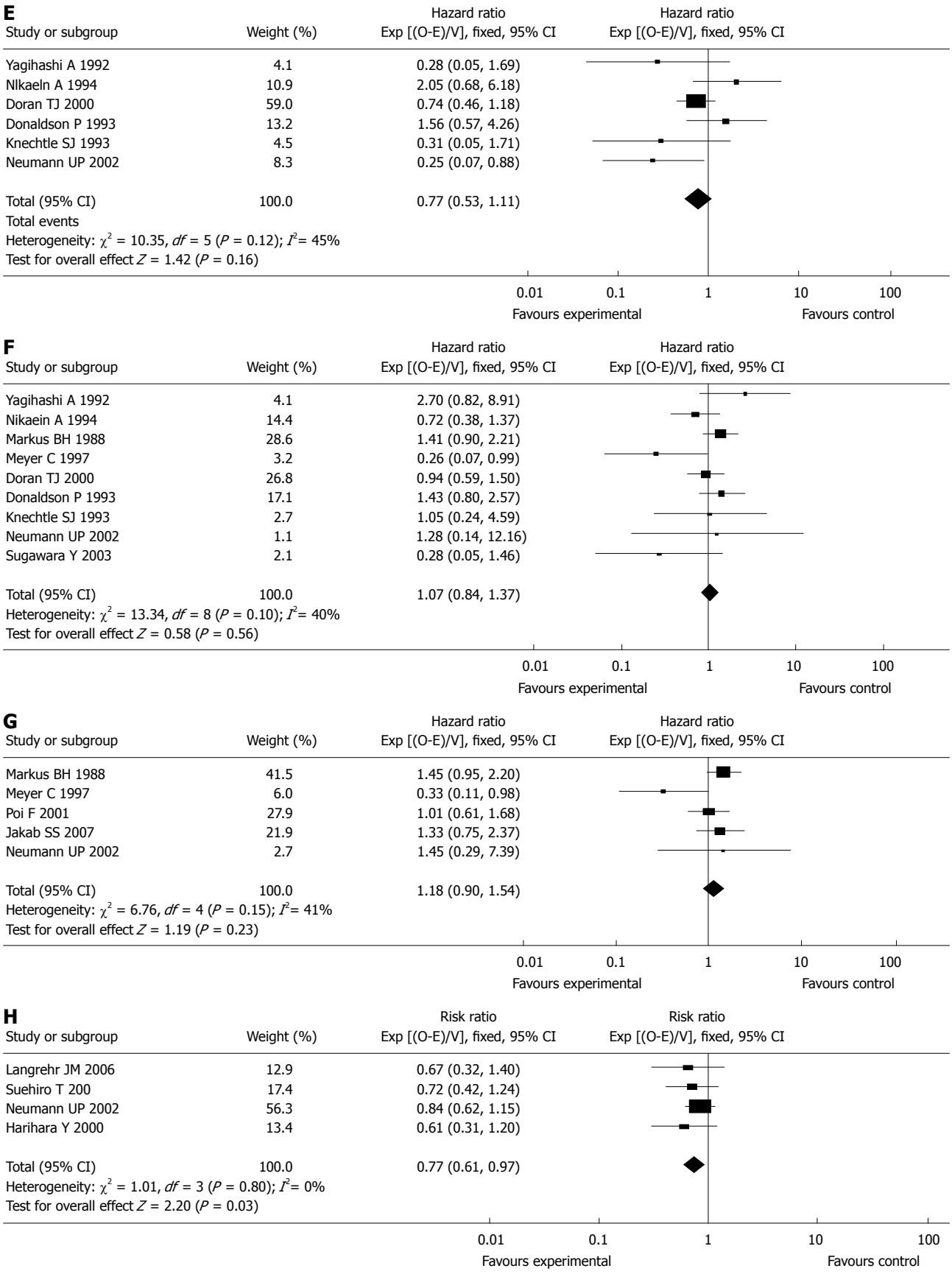


Figure 2 Meta-analysis of cohort trials comparing the effect of different mismatches of human leukocyte antigen epitopes on graft survival and acute rejection. A: 0-2 *vs* 3-6 mismatches of human leukocyte antigen (HLA)-A, B, DR epitopes on 1-year graft survival; B: 0-2 *vs* 3-6 mismatches of HLA-A, B, DR epitopes on 5-year graft survival; C: 0 *vs* 1-2 mismatches of HLA-A epitopes on 1-year graft survival; D: 0 *vs* 1-2 mismatches of HLA-A epitopes on 5-year graft survival; E: 0 *vs* 1-2 mismatches of HLA-B epitopes on 1-year graft survival; F: 0 *vs* 1-2 mismatches of HLA-DR epitopes on 1-year graft survival; G: 0 *vs* 1-2 mismatches of HLA-DR epitopes on 5-year graft survival; H: 0-2 *vs* 3-6 mismatches of HLA-A, B and DR epitopes on acute rejection.

3 other risk factors (cold ischemia time greater than 15 h, pretransplantation elevation of aspartate transaminase, and older donor age) are less readily explained, but suggest that nonallogeneic and allogeneic immunological injury may be related. Both a long cold ischemia time and older donor age predispose an allograft liver to injury shortly after transplantation, which evokes immunological reactions that are not necessarily triggered by allogeneic differences.

Although a meta-analysis may provide a high level of scientific evidence, it is important to realize the limitations of interpreting results of meta-analyses. One major limitation to the meta-analysis is that inferences are based on aggregate analysis of relatively heterogeneous studies. We acknowledge the potential heterogeneity of combining studies from different centers in different geographic locations with different treatment protocols. In our systematic review, results obtained from each study were considered to be homogeneous (heterogeneity test was $P > 0.10$ and $I^2 < 50\%$ in all available studies) in spite of there being no RCTs in this meta-analysis. Although we did not investigate through meta-regression any differences in the use of immunosuppressants or differences in study centers, the treatment protocols were nearly the same: cyclosporine or tacrolimus, azathioprine and prednisolone and no mycophenolate mofetil were used (Table 1).

Additionally, some studies did not report results with the measures that we chose for data extraction. It is the second limitation we must deal with. Survival rates under 1-year or 5-year were extracted by special software from survival curves if they was not shown in articles directly. We did not even obtain any data from some cohort studies, but including or excluding these articles also did not affect our conclusions.

The length of post transplantation follow-up was another limitation of many of the trials that we analyzed. Although most trials reported follow-up of some patients up to 5 years or even longer, some reported follow-up only to 1 year or 6 mo. Long-term graft survival, including HBV, HCV and hepatocellular carcinoma recurrence, may only become apparent or more pronounced after many years of post liver transplantation follow-up, and hence we may have underestimated the mortality in our study. In other words, we may have overestimated the role of HLA mismatching in liver graft loss.

Despite these limitations, our meta-analysis suggests that a lower number of HLA mismatching did reduce the incidence of acute rejection. The degree of HLA mismatching had no significant effect on 1-year and 5-year graft survival. Performing good donor-recipient HLA matching appears to be associated with a reduction in the incidence of acute rejection. Thus to obtain a shorter recovery time and avoid more rejection post transplantation, HLA matching examinations should be considered before surgery.

COMMENTS

Background

The role of human leukocyte antigen (HLA) matching between donor and recipient in organ transplant rejection and survival has been widely studied and proven to increase graft survival and to reduce the incidence of acute or chronic rejection. In contrast, major histocompatibility complex analysis is not routinely performed in liver transplantation because its importance remains controversial.

Research frontiers

Different groups have reported disparate results on the effect of HLA matching: some patients acquired benefit from high degrees of HLA matching but concern has been voiced about a greater likelihood of recurrence of primary disease with good HLA compatibility.

Innovations and breakthroughs

This is the first systematic review and meta-analysis on the effect of HLA mismatching in short and long term liver graft outcome and acute rejection. Importantly, the authors have some different conclusions compared to traditional views. Good donor-recipient HLA matching appears to be associated with a reduction in the incidence of acute rejection although there is no effect on 1-year and 5-year survival rates.

Applications

The percentage of graft survival was extracted by "Engauge Digitizer" from survival curves if the raw data was not presented. All statistical analyses were performed using Review Manager 5.0 which was a new program for determining HR.

Peer review

The authors aimed to assess the effect of HLA mismatching in liver graft outcome and acute rejection from available cohort studies by a systematic review and meta-analysis. The design of the study is rational and reliable, and the statistical methods used are appropriate. The article is also well organized. The conclusion may provide reliable and valuable information for clinical practice.

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