Original Article

The correlation between human leucocyte antigen amino acid residue matching before keratoplasty and postoperative rejection: a systematic review and meta-analysis

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Background: At present, corneal transplantation has become the main surgical method for infectious keratitis. However, the rejection of corneal graft after operation leads to graft opacity, which is an important reason for the failure of transplantation. There is no unified conclusion whether the rejection can be reduced by matching human leucocyte antigen (HLA) before operation. The purpose of this meta-analysis is to explore the correlation between HLA locus matching and corneal transplantation rejection, so as to provide evidence-based medical evidence for clinical corneal transplantation in the treatment of infectious keratitis.

Methods: Search English databases, such as PubMed, Medline, Embase and Evidence-based Medicine Library by computer; Chinese databases, such as China Biomedical Literature Database, China Knowledge Network (CNKI) database, Wanfang database, Weipu database, and Google Academic database. According to Cochrane Handbook 5.0 risk assessment table, two researchers made random sequence random allocation method, blind method, allocation scheme hiding, integrity of data results and quality score of research results. The bias risk evaluation of Rev Man 5.3 software was used to evaluate the risk bias of the references.

Results: A total of 5 literatures were included, and 725 eyes underwent penetrating keratoplasty, all of which were randomized controlled trials (RCTs). The quality of the included articles was medium to high quality. A meta-analysis of four HLA-A matching articles showed odds ratio (OR) =0.28, 95% confidential interval (CI): (0.15, 0.51), significance test Z=4.08, P<0.0001, and the difference was statistically significant. Meta-analysis was performed on four HLA-B matching articles and showed OR =0.50, 95% CI: (0.27, 0.89), significance test Z=2.33, P=0.02, and the difference was statistically significant. Meta-analysis of four HLA-DR matching articles showed OR =0.69, 95% CI: (0.41, 1.17), significance test Z=1.39, P=0.17, and the difference was not statistically significant.

Discussion: In patients with infectious keratitis undergoing corneal transplantation, preoperative matching of HLA-A, HLA-B, and HLA-DR sites played an important role in corneal transplantation. Preoperative HLA matching is of clinical significance.

Keywords: Infectious keratitis; human leucocyte antigen (HLA); corneal transplantation; rejection; meta-analysis

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Introduction

Corneal disease is a common disease in ophthalmology. Epidemiological survey shows that there are nearly 10,000 blind people in China at present, which has become the second leading cause of blindness. However, only about 5,000 corneal transplants are performed every year (1,2). The main causes of corneal blindness are corneal trauma and corneal infection. Besides mechanical injuries, corneal chemical injuries, thermal burns and explosive injuries are also common. Infectious keratitis is mostly caused by external pathogenic microorganisms invading the ocular surface directly. When the inflammation is severe, the cornea will be visibly cloudy (3-5). Infectious keratitis is still a common blinding eye disease, and about 20% of the blind people are blind due to eye infection. Its incidence is high. If the infection is not controlled in time, severe consequences such as corneal perforation and endophthalmitis often occur in the later stage (6).

At present, when the cornea is gradually thinned or perforated, the integrity and residual vision of eyeball can be preserved by corneal transplantation (7,8). The rejection of corneal graft after operation leads to graft opacity, which is one of the important reasons for the failure of transplantation, especially for high-risk transplant patients with inflammation or neovascularization, and the immune rejection rate is over 60%. Immunosuppressants are usually used to improve the survival rate of corneal grafts, but there will be many side effects if immunosuppressants are used for a long time. With the development of immunology and molecular biology, the research on the prevention and treatment of immune rejection after corneal transplantation has also made progress in recent ten years. A large number of studies have reported the role of human leucocyte antigen (HLA) matching in corneal transplantation. Holán *et al.* [1996] (9) statistically analyzed 419 patients and found that although the rejection rate of HLA-A, B and DR matched groups is lower than that of mismatched groups, there is no statistical difference. Instead, it was found that blood type matching was meaningful in reducing rejection. Fink *et al.* [1994] (10) studied the correlation between HLA-A, B, DR and cross-matching between corneal transplant patients and donors. The results showed that the relationship between rejection, mismatch and serum cross-positive could be neglected. On the contrary, blood group mismatch has an effect on rejection.

In corneal transplantation, there are many studies on whether HLA matching can reduce rejection, but the conclusions are not unified. Meta-analysis is a statistical method used to compare and synthesize the research results of the same scientific problem. Whether the conclusions are meaningful or not depends on the quality of the included research, and it is often used for quantitative combination analysis in systematic review. The innovation of this study lies in the application of Meta-analysis method to evaluate the related clinical randomized controlled studies in the past, aiming at exploring the correlation between HLA-A, B and DR and corneal transplant rejection, and providing evidence-based medicine basis for clinical corneal transplant surgery to treat infectious keratitis. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-268/rc).

Methods

Articles retrieval

English databases including the United States National Library of Medicine (PubMed), Medline, Embase, and Cochrane library were searched by combination of the terms “corneal transplantation”, “penetrating keratoplasty”, “graft rejection”, “histocompatibility antigens”, and “HLA antigens”. Chinese database including the China Biomedical Literature database, China Knowledge Network (CNKI) database, Wanfang database, Weipu database, and Google Scholar were searched by combination of the terms “infectious keratitis”, “corneal transplantation”, “HLA matching”, and “rejection”. The retrieval time was from the establishment of the database to August 20, 2021, and Rev Man 5.3 software provided by the Cochrane system was used to evaluate the quality of the literature.

The above search terms were combined freely for searching, and after multiple searches to confirm the articles, the search engine was adopted to trace the confirmed articles to obtain the latest research progress and conduct data collection.

Inclusion and exclusion criteria of the included articles

Inclusion criteria were given as follows: articles which were randomized controlled trials (RCTs) to explore the correlation between HLA gene matching and corneal transplantation rejection; articles mentioning the research objects were more than 18 years old; articles whose research subjects were high-risk corneal transplantation

patients; articles mentioning a postoperative follow-up time of more than 6 months; and articles with preoperative corneal transplantation patients with HLA matching in the experimental group and unmatched corneal transplantation patients in the control group.

Exclusion criteria were defined as follows: articles involving research on non-HLA-A, B, or DR locus genes; articles involving animal models; studies involving pregnant or lactating women; reviews, conferences, and similar articles; articles involving patients with malignant tumors; and articles which were repeated publications or with incomplete data.

Data extraction

Two researchers conducted evaluations based on uniform quality standards and used uniform Excel spreadsheets to extract literature data. The data extracted included: the title of the article, the first author, and the year of publication of the article; general information of the research object (such as age and gender); the source of the research object, sample size, and observation indicators.

Quality evaluation and bias risk assessment

The Cochrane Handbook 5.0 risk assessment form was adopted to evaluate the quality of included articles. The evaluation indicators included a random allocation method of random sequencing, blind method, allocation plan hiding, completeness of data results, and quality scores. The quality and authenticity of the included RCT articles were evaluated, and judgments of "high-risk bias", "low-risk bias", and "unclear" were made on the above five aspects. Two experts were required to conduct a bias risk assessment at the same time, and in cases of inconsistency, the result was determined through discussion or arbitration of a third expert.

Statistical analysis

StataSE12.0 software was adopted for statistical analysis and Rev Man 5.3 software's risk of bias assessment chart was applied to assess the risk bias of the included articles. Odds ratio (OR) and its 95% confidential interval (CI) were selected as the statistical analysis quantities of counting data, and the heterogeneity among the results of each study was evaluated by the χ^2 test and the I^2 test. When $P>0.1$ and $I^2<50\%$, the fixed effects model was used for meta-analysis, and when $P<0.1$ and $I^2>50\%$, the random effects model was used. The result of the combined effect test was expressed as the Z value, and the P value was obtained according to the Z value.

Results

Retrieval results and basic information of included articles

A total of 310 articles were screened from the databases. Of the 310, 78 repeatedly published, 45 were unqualified articles, and 12 were excluded from other reasons, leaving 175 articles for further analysis. After the titles and abstracts were read, 126 articles were eliminated, leaving 49, and after 32 unqualified articles such as literature, review and conference were excluded, 17 articles remained. A further 12 articles were excluded because they did not contain the required observation index data (the observation index was not HLA-A, B, C site matching), leaving five articles for meta-analysis (*Figure 1*).

A total of 725 eyes underwent penetrating corneal transplantation, and the sample size ranged from 40 to 459 eyes. The basic characteristics of the included articles and various observation data are shown in *Table 1*. Among the five articles included, four had a score of 4–7, and one had a score of 0–3. Five articles described in detail the first author, publication year, number of eyes, follow-up time (months), and observation indicators of the matching group and the control group.

Bias risk assessment results of included articles

The Cochrane Handbook 5.0 was used to evaluate the risk of bias, and a risk of bias ratio chart was drawn (*Figures 2,3*). Among the five articles, three were randomly grouped and two were grouped by a computer random number table method. None of the articles mentioned whether to use allocation hiding, while some of the subjects in two articles withdrew from the experiment due to adverse reactions. There were no incomplete data and selective reports, and the quality of the included articles was medium to high quality.

Meta-analysis of the number of eyes undergoing transplant rejection after corneal transplantation HLA-A matching and non-matching

A total of four articles (11-13,15) (88 eyes in the HLA-A matching group and 213 eyes in the control group) conducted a controlled study on the number of eyes with

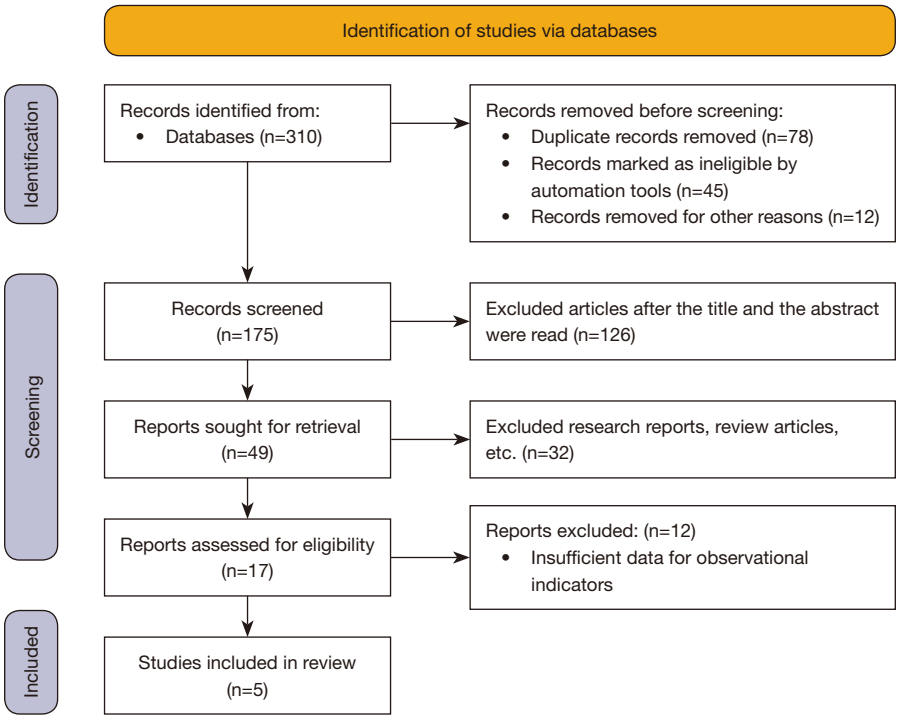

Figure 1 Flow chart of articles retrieval.

Table 1 General data of included articles

The first author	Year of publication	Number of eyes	Follow-up time (months)	Matching group			Control group		
				HLA-A	HLA-B	HLA-DR	HLA-A	HLA-B	HLA-DR
Bartels (11)	2001	64	35	5/26	5/15	7/25	16/37	14/44	14/39
Khaireddin (12)	2003	459	31	7/26	10/29	17/36	61/122	58/119	50/110
Morita (13)	1998	81	32	2/16	2/12	2/10	16/34	15/37	16/41
Munkhbat (14)	1997	81	12	–	–	3/14	–	–	19/37
Ozdemir (15)	1986	40	24	2/20	2/20	–	8/20	8/20	–

HLA-A, human leucocyte antigen-A; HLA-B, human leucocyte antigen-B; HLA-DR, human leucocyte antigen-DR.

rejection after corneal transplantation in the two groups, all of which were RCTs. Meta-analysis was performed on four articles, which showed P=0.76 and I^2=0%, showing statistical homogeneity. The fixed-effects model was adopted for meta-analysis, and showed the OR =0.28, 95% CI: (0.15, 0.51), significance test Z=4.08, P<0.0001, and the difference was statistically significant (*Figure 4*), indicating that the number of eyes in the HLA-A matching group after corneal transplantation rejection was less than that in the control group.

Excluding two articles by sensitivity analysis had no significant effect on overall heterogeneity. The inverted funnel chart showed the data was relatively concentrated, and the circles in some articles were basically symmetrical with the center line, indicating the research accuracy was high and there was no publication bias (*Figure 5*).

Meta-analysis on the number of eyes undergoing transplant rejection after corneal transplantation HLA-B matching and non-matching

A total of four articles (11-13,15) (76 eyes in the HLA-B

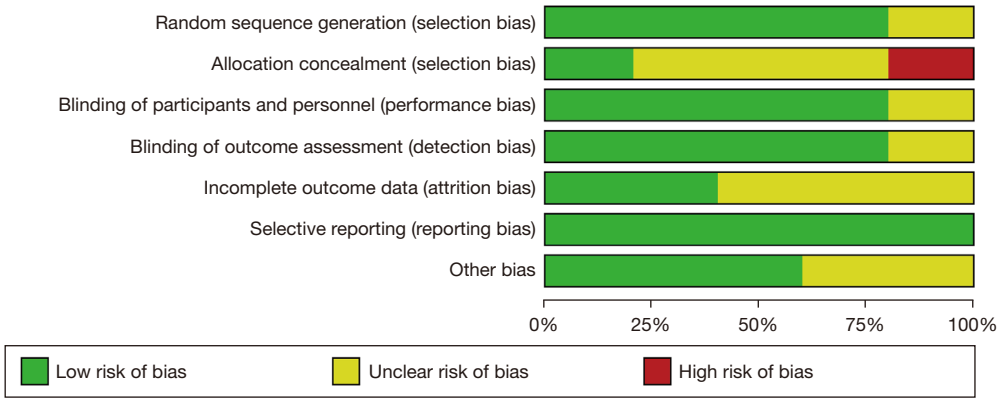

Figure 2 Risk bias evaluation results of included articles.

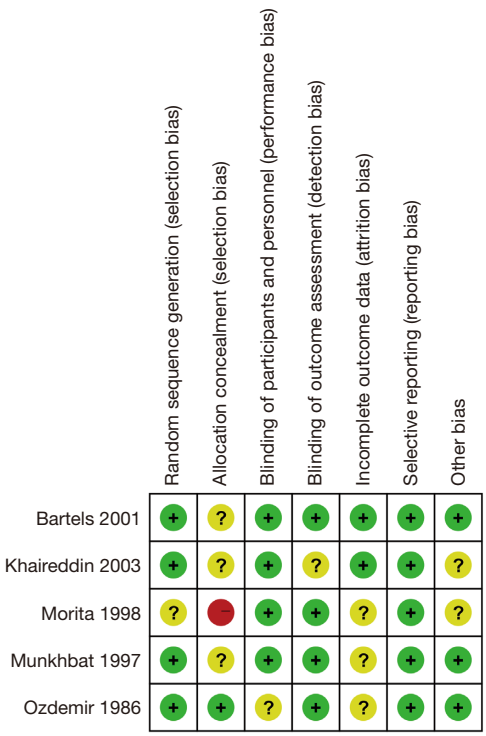

Figure 3 Distribution of multiple risk bias evaluation results corresponding to the included articles. "+": low risk; "–": high risk; "?": unclear.

matching group and 220 eyes in the control group) conducted a controlled study on the number of eyes with rejection after corneal transplantation in the two groups, all of which were RCTs. Meta-analysis was performed on four articles, which showed P=0.32 and I^2=14%, showing statistical heterogeneity. The fixed-effects model was adopted for meta-analysis, and showed the OR =0.50, 95% CI: (0.27, 0.89), significance test Z=2.33, P=0.02, and the difference was statistically significant (*Figure 6*), indicating the number of eyes in the HLA-B matching group after corneal transplantation rejection was less than that in the control group.

Excluding two articles by sensitivity analysis had no significant effect on overall heterogeneity. The inverted funnel chart showed the data was relatively concentrated, and the circles in some articles were basically symmetrical with the center line, indicating the research accuracy was high and there was no publication bias (*Figure* 7).

Meta-analysis on the number of eyes undergoing transplant rejection after corneal transplantation HLA-DR matching and non-matching

A total of four articles (11-14) (85 eyes in the HLA-DR matching group and 227 eyes in the control group) conducted a controlled study on the number of eyes with rejection after corneal transplantation in the two groups, all of which were RCTs. Meta-analysis was performed on four articles, which showed P=0.31 and I^2=16%, showing statistical homogeneity. The fixed-effects model was adopted for meta-analysis, and showed the OR =0.69, 95% CI: (0.41, 1.17), significance test Z=1.39, P=0.17, and the difference was statistically significant (*Figure 8*).

Excluding two articles by sensitivity analysis had no significant effect on overall heterogeneity. The inverted funnel chart showed the data was relatively concentrated, and the circles in some articles were basically symmetrical with the center line, indicating the research accuracy was high and there was no publication bias (*Figure 9*).

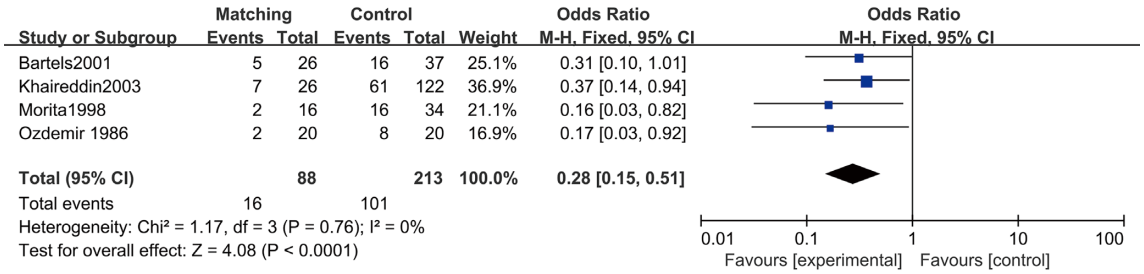

Figure 4 Comparison of the number of eyes with transplant rejection in corneal transplantation HLA-A matching group and control group. HLA-A, human leucocyte antigen-A; df, degree of freedom; CI, confidence interval.

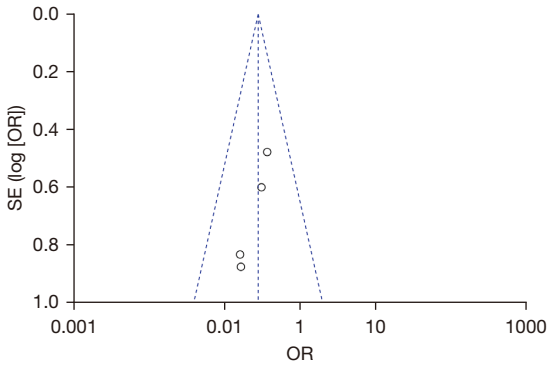

Figure 5 Funnel chart of the corneal transplantation HLA-A matching group and the control group after transplantation rejection. HLA-A, human leucocyte antigen-A; SE, standard error; OR, odds ratio.

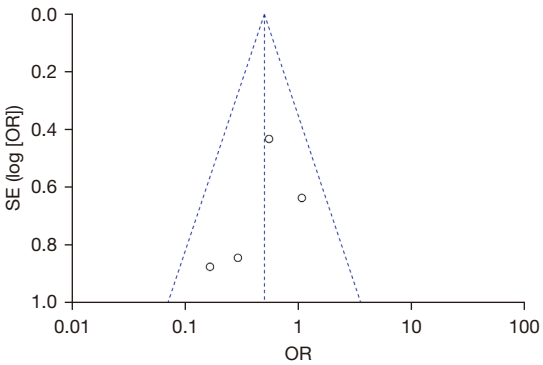

Figure 7 Funnel chart of the corneal transplantation HLA-B matching group and the control group after transplantation rejection. HLA-B, human leucocyte antigen-B; SE, standard error; OR, odds ratio.

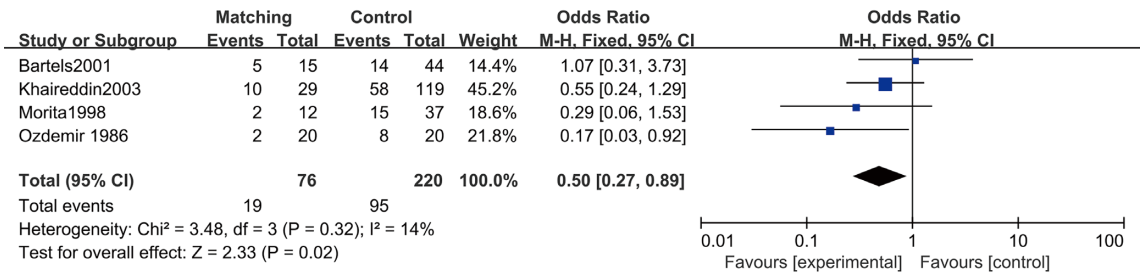

Figure 6 Comparison on the number of eyes with transplant rejection in corneal transplantation HLA-B matching group and control group. HLA-B, human leucocyte antigen-B; df, degree of freedom; CI, confidence interval.

Discussion

HLA matching before surgery can avoid immune rejection after corneal transplantation. Previously published articles related to HLA matching before corneal transplantation were screened for meta-analysis on the correlation between HLA matching and postoperative immune rejection from the perspective of evidence-based medicine. The meta-analysis results of this study showed the number of rejected eyes in the matching group and the control group was statistically significant [OR =0.28, 95% CI: (0.15, 0.51), significance test Z=4.08, P<0.0001]. It showed the higher

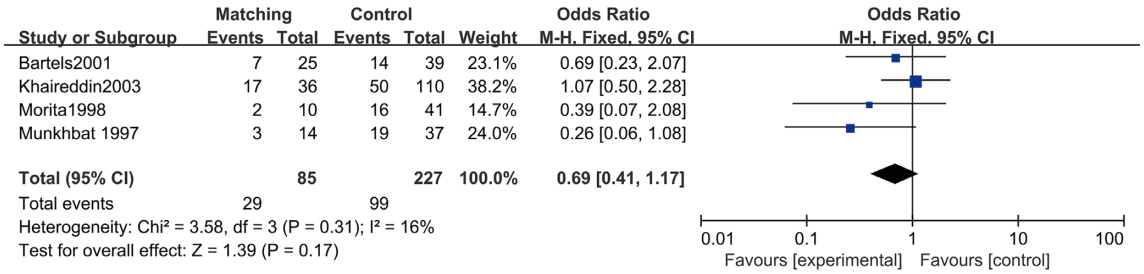

Figure 8 Comparison of the number of eyes with transplant rejection in corneal transplantation HLA-DR matching group and control group. HLA-DR, human leucocyte antigen-DR; df, degree of freedom; CI, confidence interval.

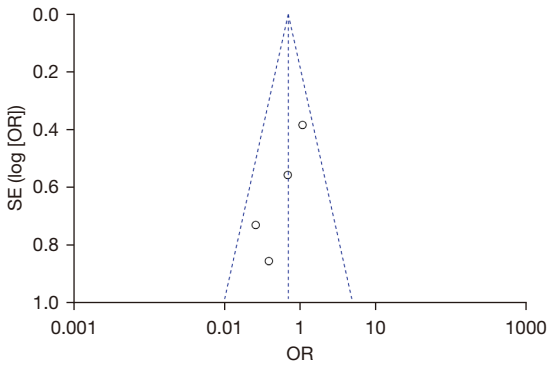

Figure 9 Funnel chart of the corneal transplantation HLA-DR matching group and the control group after transplantation rejection. HLA-DR, human leucocyte antigen-DR; SE, standard error; OR, odds ratio.

the number of selected donor sites matched, the higher the survival rate after cross-matching. The survival rate was as high as 90% after 24 months of follow-up, which indicated the number of HLA matches had a certain correlation with the incidence of rejection.

In HLA-B locus matching, the difference in the number of eyes with rejection after the matching group and the control group was statistically significant [OR =0.50, 95% CI: (0.27, 0.89), significance test Z=2.33, P=0.02]. The mechanism may be the mismatch of the HLA-B locus, and the donor cells of HLA-I antigen may be the target of CD8+ cytotoxic T lymphocytes (16-18). In patients with infectious keratitis, the incidence of rejection in the HLA-DR matching group was lower than in the control group, but the difference was not statistically significant [OR =0.69, 95% CI: (0.41, 1.17), significance test Z=1.39, P=0.17]. Capozzi *et al.* (19) reported HLA-DPB1 had a positive effect on reducing rejection after corneal transplantation, but not HLA-DR matching, which may be due to the small number of samples included. Armitage *et al.* (20) reported HLA-DR matching can significantly improve the corneal survival rate after transplantation, and the mechanism of action may be that the donor cells and HLA-II antigens trigger the delayed hypersensitivity response mediated by the host $CD4^+$ T helper lymphocytes. In addition, infection, rejection, or the inflammatory response produced by the transplantation process itself may cause the corneal endothelium to mediate the expression of HLA-II antigens (21-23). Therefore, if the donor and host HLA-DR sites do not match, it is very easy to cause a delayed hypersensitivity rejection activated by host $CD4^+$ T lymphocytes.

Among the five articles included in this study, three were randomly grouped, and two were grouped using a computer random number table method. No articles mentioned whether to use allocation concealment, there were no incomplete data and selective reports, and the quality of the included literature was medium to high quality. However, the limitations of this study which are summarized as follows: First, the number of included articles and the number of samples were limited. Second, there was potential publication bias and language bias. Third, there were few RCTs included in the articles and a lack of blinding methods for infectious keratitis patients, which may have caused research object performance and detection bias.

Conclusions

This meta-analysis searched the literature related to corneal transplantation preoperative HLA amino acid residue matching and postoperative rejection. In patients with infectious keratitis undergoing corneal transplantation, preoperative matching of HLA-A, HLA-B, and HLA-

DR sites plays an important role. However, the limited number of articles and samples included in this meta-analysis make it difficult to form a definitive conclusion. Further multi-center, large-sample RCTs are required to evaluate the correlation between HLA gene matching and corneal transplantation rejection more scientifically and systematically, to provide more reliable evidence-based medical evidence for infectious keratitis research and clinical treatment.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-268/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-268/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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