·Clinical Research·

# Risk factors for corneal graft failure and rejection in penetrating keratoplasty

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## Abstract

• AIM: To evaluate risk factors of graft failure and allograft rejection after penetrating keratoplasty (PK).

• METHODS: Clinical data of PKs on 224 eyes (212 patients) from 1996 to 2006 were studied retrospectively. The graft survival rate and rejection-free survival rate over 10 years were estimated with Kaplan-Meir's life table, and differences between levels of each factor were compared with log-rank test. Cox regression was also performed to further assess the impact of related clinical factors on the prognosis of the corneal graft.

• RESULTS: The overall rates of graft survival and rejection-free graft survival at 10 years after PK were 81.4% and 78.2% respectively. Relatively higher risk of graft failure was associated with corneal vascularization, regraft, aphakia or pseudophakia, presence of anterior or posterior synechia, long (≥90 minutes ) operation time and older (≥60 years) age of recipient. Relatively higher risk of rejection was associated with corneal vascularization and long operation time. Cox regression analysis showed corneal vascularization ($RR$ = 2.46, $P$=0.04), regraft ($RR$=5.67, $P$<0.01), aphakia ($RR$ = 3.64, $P$ <0.05), or pseudophakia ($RR$ =6.83, $P$ <0.01), presence of anterior ($RR$ =2.76, $P$ = 0.05) or posterior synechia ($RR$=3.12, $P$=0.05) were independent risk factors for corneal graft failure.

• CONCLUSION: The risk factors for graft failure after PK were corneal vascularization, regraft, aphakia or pseudophakia, presence of anterior or posterior synechia. The risk factors after PK for allograft rejection were corneal vascularization and long operation time.

• KEYWORDS: penetraing keratoplasty; graft failure; allograft rejection; risk factor

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## INTRODUCTION

Despite the continuous evolvement of new surgical techniques, such as deep lamellar keratoplasty (DLEK)[1], penetrating keratoplasty (PK) remains to be the most common form of corneal transplantation [2]. Furthermore, owing to the development of microsurgical instrumentations and postoperative management in recent years, indications for PK have been extended continuously. In this study, the authors analyzed retrospectively the graft survival rate and rejection-free graft survival rate to the main corneal diseases in a single center and determined the preoperative risk factors leading to a poor outcome of penetrating keratoplasty.

## MATERIALS AND METHODS

**Patients** From November 1996 to October 2006, 236 PKs were performed in 222 patients (144 males, 78 females) at the Department of Ophthalmology in General Hospital of Chinese PLA. The 12 cases that lacked complete information on dependent variables used in this analysis were excluded from the study. Finally, this analysis was carried out on a total of 224 PKs of 212 patients (138 males, 74 females). The mean age was 36.6± 16.7 (2-83) years. The preoperative diagnoses included corneal leucoma due to trauma (mechanical or chemical, 87, 39%), keratoconus (36, 16%), herpes keratitis (14,6%), bacterial and fungal keratitis (12,5%), corneal dystrophies and degenerations (48, 21%), bullous keratopathy (16,7%) and others(11,5%). Demographic data for the 224 PKs are shown in Table 1.

**Surgical Pocedures and Postoperative Medical Treatment** Donor eyes were enucleated aseptically and then maintained in preservation media. Transplantations were performed within 24 hours in most of the cases. The donor buttons were punched out of the endothelial side by trephines with a diameter equal to 0.25 to 0.50mm larger

**Table 1 Analyzed factors for 224 penetrating keratoplasty** (*n*,%)

| Factors | Factors levels | Number of eyes (%) |
|---|---|---|
| Regraft | Presence | 39(17) |
| | Absence | 185(83) |
| Corneal vascularization | 0 | 102(46) |
| | 1 | 46(21) |
| | 2 | 54(24) |
| | ≥3 | 22(9) |
| Lens status | Phakia | 165(74) |
| | Aphakia | 35(15) |
| | Pseudophakia | 24(11) |
| Anterior synechia | Absence | 182(81) |
| | Presence | 42(19) |
| Posterior synechia | None | 196(88) |
| | Positive | 28(12) |
| Suture technique | Interrupt | 146(65) |
| | Continuous | 62(28) |
| | Combined | 16(7) |
| Graft size | <8mm | 182(81) |
| | ≥8mm | 42(19) |
| Operation time | <90min | 117(52) |
| | ≥90min | 107(48) |
| Recipient age | <60years | 168(75) |
| | ≥60years | 56(25) |

than that of the recipient. The mean diameter of the graft was 7.34 ±0.50 (6.00-10.00)mm, and the diameter of the corneal graft was 0.25- 0.50mm larger than that of the recipient cornea. The grafts were sutured to the recipient corneas with preplaced sutures at 3, 6, 9 and 12 o'clock followed by sixteen continuous or discontinuous 10-0 nylon sutures. Lensectomy, anterior vitrectomy or intraocular lens implantation were performed when necessary. Patients received a subconjunctival injection of dexamethasone and gentamicin at the end of surgery. Topical treatment including antibiotics, corticosteroids and cyclosporin A eye ointment or eyedrops was used routinely in all patients. Prednisone was taken orally at the dose of 1mg/(kg•d) for 1 month and then tapered at the discretion of the treating physician. The corneal sutures were usually removed at 6-12 months after surgery.

**Patient Follow –up and Transplant Outcome** Patients were followed up every 1 to 2 months during the first year after surgery, and then once at 3-12 months. The mean follow-up time was 54.6±38.4(10-131) months. Graft failure was defined as an irreversible loss of central graft clarity

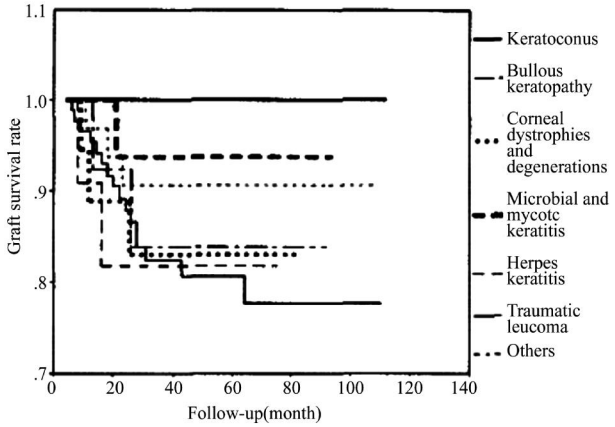


**Figure 1 Kaplan–Meir survival rate in different corneal diseases**

and was determined clinically by using a slit-lamp biomicroscope. Graft rejection was defined as an edematous graft occurred more than 2 weeks after the surgery and showed at least one of the following signs: ① an endothelial rejection line, ② infiltrating keratic precipitates, and ③ anterior segment inflammation [3]. The extent of corneal vascularization was graded into four stages: 0, no vessels in any quadrant; 1, vessels within one quadrant; 2, vessels in two quadrants; and 3, vessels in three or more quadrants.

**Statistical Analysis** Data were presented as mean-SEM for continuous variables and as absolute frequencies for categorical variables. Graft survival rate and rejection-free graft survival rate were estimated by Kaplan-Meier's method and compared among different factor-levels with log-rank test. Cox regression was performed to further assess the impact of related clinical factors on the prognosis of the corneal graft. Statistical significance was set as $P<0.05$, and analyzed using SPSS 10.0 software.

**RESULTS**

The overall estimated graft survival rate over 10 years after PK was 81.4%. The respective survival rates of different preoperative diagnoses are shown in Figure 1, with the highest in keratoconus (100%) and the lowest in corneal leucoma due to trauma(76.4%). The overall estimated rejection-free graft survival rate over 10 years after PK was 78.2%. The respective graft survival rate and rejection-free graft survival rate over 10 years for different patient groups acording to their factor levels are shown in Table 2 and Table 3. The respective estimated relative risks of graft failure and rejection-free graft failure are also shown in Table 2 and Table 3. Factors associated with graft failure include corneal vascularization, regraft, aphakia or pseudophakia, posterior or anterior synechia, long (≥90 minutes) operation time,

**Table 2 Graft survival rates in 10a after PK and relative risks** (RR)

| Factors | Factor levels | Survival rate (%) | Log-rank value | *P* | RR |
|---|---|---|---|---|---|
| Regraft | Presence | 66.8 | 19.6 | <0.001 | 1 |
| | Absence | 82.4 | | | 1.89 |
| Corneal vascularization | 0 | 86.4 | 17.3 | <0.001 | 1 |
| | 1 | 78.3 | | | 1.60 |
| | 2 | 71.2 | | | 2.12 |
| | ≥3 | 57.6 | | | 3.12 |
| Lens status | Phakia | 84.2 | 24.2 | <0.001 | 1 |
| | Aphakia | 67.4 | | | 2.06 |
| | Pseudophakia | 56.2 | | | 2.77 |
| ior synechia | Absence | 86.2 | 25.4 | <0.001 | 1 |
| | Presence | 58.4 | | | |
| sterior synechia | Absence | 82.3 | 18.8 | <0.001 | 1 |
| | Presence | 58.4 | | | 3.01 |
| Suture technique | Interrupt | 76.6 | 1.64 | 0.42 | |
| | Continuous | 80.4 | | | |
| | Combined | 81.6 | | | |
| Graft size | <8mm | 81.6 | 0.04 | 0.85 | |
| | ≥8mm | 78.4 | | | |
| Operation time | <90min | 83.8 | 18.4 | <0.001 | 1.95 |
| | ≥90min | 68.4 | | | |
| Recipient age | <60years | 84.4 | 16.6 | | 1 |
| | ≥60years | 71.2 | | | 1.85 |

**Table 3 Rejection-free graft survival rates in 10a after PK and relative risks** (RR)

| Factors | Factor levels | Rejection-free graft survival (%) | Log-rank value | *P* | RR |
|---|---|---|---|---|---|
| Regraft | Presence | 68.2 | 3.84 | <0.001 | |
| | Absence | 72.4 | | | |
| Corneal vascularization | 0 | 87.0 | 21.3 | <0.001 | 1 |
| | 1 | 72.3 | | | 2.13 |
| | 2 | 70.2 | | | 2.29 |
| | ≥3 | 59.6 | | | 3.11 |
| Lens status | Phakia | 77.2 | 0.68 | <0.001 | |
| | Aphakia | 82.4 | | | |
| | Pseudophakia | 76.8 | | | |
| Anterior synechia | Absence | 79.6 | 0.54 | <0.001 | |
| | Presence | 76.2 | | | |
| Posterior synechia | Absence | 78.3 | 0.18 | <0.001 | |
| | Presence | 77.4 | | | |
| Suture technique | Interrupt | 77.6 | 0.64 | 0.42 | |
| | Continuous | 75.8 | | | |
| | Combined | 80.2 | | | |
| Graft size | <8mm | 81.6 | 2.12 | 0.85 | |
| | ≥8mm | 75.4 | | | |
| Operation time | <90min | 82.8 | 7.62 | <0.001 | 1 |
| | ≥90min | 65.1 | | | 2.03 |
| Recipient age | <60years | 78.8 | 0.53 | | |
| | ≥60years | 81.2 | | | |

and older (≥60 years) recipient age. Factors associated with graft rejection includes corneal vascularization and long (≥ 90 minutes) operation time. Cox regression model showed only corneal vascularization (*RR*=2.46, *P*=0.04), regraft (*RR*=5.67, *P*<0.01), aphakia (*RR*=3.64, *P*<0.05) or pseudophakia (*RR*= 6.83, *P*<0.01), presence of anterior (*RR*= 2.76, *P*= 0.05) or posterior synechia (*RR*=3.12, *P*= 0.05) were independent risk factors for corneal graft failure. There was no significant association between graft failure or allograft rejection and graft size or suture technique, respectively.

## DISCUSSION

Corneal transplantation has been the most successful one in human organ transplantations, mainly because of the existence of the immune privilege of the cornea[4]. However, graft failure still occurs in about 3%-20% of PKs, with the allograft rejection as the major cause [3, 5-7]. The reported risk factors, besides the vitality of the donor graft per se, for graft failure include: corneal vascularization, previous transplant numbers, suture technique, preoperative glaucoma, presence of anterior or posterior synechia of iris, presence of aphakia or pseudophakia, graft size, operation time, blood group ABO incompatibility, and human leukocyte antigens incompatibility. Risk factors for rejection in PK were reported to be corneal vascularization, previous transplant number and suture technique[6-8]. In this study, using both the life table method and the stratified analysis method in the Cox multiple regression model, we tried to analyze the major factors which might affect the survival rate of PK among various factors suspected of worsening the outcome of penetrating keratoplasty. However, because it is not a routine in our clinical work to examine both the donor's and the recipient's ABO blood type and HLA antigens, we could not evaluate these two factors. In addition, postoperative medication and management also exert great influence on the outcome of graft survival rate, especially the occurrence of graft rejection. Nevertheless, the administration of corticosteriods and cyclosporine, including the dosage, route and course was similar in our patients of PK, so we did not analyze this factor either.

In the current study, we found that corneal vascularization, regraft, presence of anterior or posterior synechia of iris and presence of aphakia or pseudophakia were independent risk factors of postoperative corneal graft survival rate, which is consistent with the results of most of the previous reports. However, using multivariate analysis, we did not find graft size, suture technique or operation time, and the recipient's

age had independent effect on the long time survival rate of corneal graft.

Compared with most of the previous reports, the estimated overall 10 years' survival rate of 81.4% in our study is relatively low. The reasons may be multifactorial. There is a relatively higher percentage of patients with high risk factors, such as postoperative vascularization and retransplantation, in our study subjects. On the other hand, it is well established that the primary cause of corneal disease is the major factor influencing the outcome of the graft, for example, keratoconus has been invariably shown to have the highest graft survival rate [2]. However, only a relatively small proportion of our patients has prognostically favorable diagnostic indications such as keratoconus or herpes keratitis, which, at least in part, may also account for the relatively poor outcome of our patients.

In summary, we found corneal vascularization, regraft, aphakia or pseudophakia, presence of anterior or posterior synechia were independent risk factors for corneal graft failure. Surgeons must take these risk factors into consideration to obtain a better prognosis for keratoplasty.

**REFERENCES**

1 Terry MA, Ousley PJ. Deep lamellar endothelial keratoplasty in the first United States patients: early clinical results. *Cornea* 2001;20:239–243

2 Suger A, Sugar J. Techniques in penetrating keratoplasty. A quarter century of development. *Cornea* 2000;19:603–610

3 Inoue K, Amano S, Oshika T, Tsuru T. Risk factors for corneal graft failure and rejection in penetrating keratoplasty. *Acta Ophthalmol Scand* 2001;79:251–255

4 Iwamoto T, Smelser GK. Electron microscope studies on the mast cells and blood and lymphatic capillaries of the human corneal limbus. *Invest Ophthalmol Vis Sci* 1965;4:815–834

5 Williams KA, Muhelberg SM, Lewis RF, Coster DJ. How successful is corneal transplantation? A report from the Australian Corneal Graft Register. *Eye* 1995; 9:219–227

6 Maguire MG, Stark WJ, Gottsch JD, Stulting RD, Sugar A, Fink NE, Schwartz A. Risk factors for corneal graft failure and rejection in the collaborative corneal transplantation studies. *Ophthalmology* 1994;101:1536–1547

7 Price FW, Whitson WE, Johns S, Gonzales JS. Risk factors for corneal graft failure. *J Refract Surg* 1996;12:134–147

8 Braude LS, Chandler JW. Corneal allograft rejection: the role of the major histocompatibility complex. *Surv Ophthalmol* 1983;27:290–305