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Original article – Clinical Sciences

Corneal Transplantation for Keratoconus: A Registry Study

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Abstract

Objective: To determine factors influencing long-term graft survival and visual acuity in 4,834 eyes of 4,060 patients receiving their first penetrating corneal graft for keratoconus.

Methods: Large cohort study from a national Register of corneal grafts, in which data were recorded prospectively and analyzed retrospectively. Main outcome measures were graft survival and Snellen visual acuity. Follow-up extended up to 23 years.

Results: Ten, twenty, and twenty-three year Kaplan-Meier survival rates of first grafts for keratoconus were 89%, 49%, and 17%, respectively. After 15 years, the graft survival rate was no better than that of all other penetrating grafts ($p=0.36$). Multivariate risk factors influencing failure of first grafts for keratoconus included time to suture removal, post-graft uveitis or microbial keratitis, corneal vascularization prior to or after graft, geographic location of surgery and follow-up (center effect), recipient age at graft, occurrence of rejection episodes, graft size and surgeon workload. The timing of bilateral grafts made no difference to the risk of rejection. A Snellen acuity of 20/40 or better at most recent follow-up was recorded in 74% of grafts.

Conclusions: Penetrating grafts performed for keratoconus exhibited better visual outcome and graft survival than grafts performed for other indications. However, Kaplan-Meier survival of first penetrating grafts for keratoconus was 17% at 23 years post-graft and had not plateaued at this time, indicating that young patients are likely to need one or more repeat grafts during their lifetime.

INTRODUCTION

Keratoconus is a common indication for penetrating keratoplasty.¹⁻² Generally, the survival of grafts performed for keratoconus is better than for other indications for graft.¹⁻⁷ In recent years, lamellar corneal transplantation has been promoted as an alternative to penetrating keratoplasty for treating keratoconus.⁸ It is thus timely to review the outcome of penetrating corneal transplantation for this condition.

Excellent short-term⁹⁻¹⁰ and long-term survival rates¹¹⁻¹³ have been reported in single-center studies, but such studies may not reflect outcomes when the procedure is practised in the broader community. Registries, in contrast, generate long-term outcome data over a wide range of clinical situations, and are useful to fill evidence gaps¹⁴ in the absence of evidence from randomized clinical trials.

The Australian Corneal Graft Registry is a large multi-center registry which follows corneal grafts performed in various settings across Australia, reflecting varying surgeon preferences for case selection, surgical technique and post-operative management in the “real-world”. We examined graft survival and best corrected visual acuity (BCVA) for 4,834 patients recorded as undergoing first penetrating keratoplasty for keratoconus from the Registry’s inception in 1985 to November 2009.

METHODS

AUSTRALIAN CORNEAL GRAFT REGISTRY

Individual surgeons across Australia handle the consent process for each patient according to local legislative requirements, permitting information to be lodged with the Australian Corneal Graft Registry. The Institutional Ethics Committee of Flinders University oversees the operations of the Registry, which are carried out in accordance with the Declaration of Helsinki.

DATA COLLECTION

All corneal grafts performed in Australia since May 1985 have been reported to the Registry. Follow-up data are collected from 634 surgeons and other practitioners at 12 month intervals until graft failure or until the death or loss to follow-up of the patient. Missing data are sought directly from the surgeon or Eye Bank, as appropriate. The information collected by the Registry has been reported elsewhere.¹⁵ Patient death is tracked using a national database of deaths. Loss to follow-up among eyes with followed penetrating grafts amounts to 30%, in addition to 24% recipient deaths.

DEFINITION OF CORNEAL GRAFT FAILURE AND MEASUREMENT OF VISUAL ACUITY

Graft failure was defined as edema and loss of clarity in a previously thin, transparent graft, or irremediable astigmatism with or without recurrent keratoconus. Primary graft non-functions were defined as grafts that never cleared in the immediate post-operative period. Any eye that was re-grafted was classified as having a previous graft failure, regardless of the reason. A rejection episode was defined as the development of inflammation, an anterior chamber reaction with corneal infiltrates (including subepithelial infiltrates) and spreading corneal edema (resulting from endothelial, epithelial or stromal rejection), or a rejection line (epithelial or endothelial) in a previously thin, transparent graft. There were no instances of simultaneous bilateral rejection. Eyes with progressive edema in the absence of inflammation were classified as exhibiting corneal endothelial cell failure of unknown cause, not as rejection. Best corrected visual acuity (BCVA) was reported with the Snellen chart, with the recipient using visual aids (that is, spectacles or a contact lens) to achieve best correction, irrespective of whether the patient was tolerant of this correction in day-to-day living.

PATIENT DEMOGRAPHICS

At the census date of November 2009, 19,529 penetrating grafts had been recorded, with 15,543 followed on at least one occasion. Follow-up was available for 4,834 *first* penetrating grafts in a given eye performed for keratoconus in 4,060 patients, 774 (19%) of whom had bilateral penetrating grafts. The frequency of bilateral grafts changed with the length of time post-graft: at ≤ 5 years or less post-graft, patients were more likely to have unilateral grafts than bilateral grafts ($p < 0.001$), whereas at > 6 years post-graft, there was no difference in the frequency of bilateral and unilateral grafts ($p = 0.07$). Follow-up ranged from 1 day to 23 years (median 35 months). Compared with the remaining cohort of penetrating grafts, loss to follow-up in eyes with grafts for keratoconus was higher (54% versus 21%), but with fewer deaths reported (3% versus 41%). The median time between transplantation in first and second eyes in the 774 patients with bilateral penetrating corneal grafts was 32 months (range 0 days-20 years).

STATISTICAL ANALYSIS

Statistical analysis was performed using Stata v9 (StataCorp, College Station, TX), with the significance level set at $p < 0.05$. The Pearson χ^2 test was used to compare observed frequencies of graft failure, rejection and vision characteristics in grafts for keratoconus with expected frequencies generated using the proportions in the cohort of all penetrating grafts. The Mann-Whitney test was used to compare age at graft and time to rejection. The relative risk (RR) for rejection in bilateral grafts was calculated using epidemiological 2x2 tables. Where appropriate, mean \pm standard deviation or 95% confidence intervals (95% CI) were reported. Graft survival amongst groups was compared with Kaplan-Meier plots, using the log-rank statistic to test statistical significance. Trial time was defined as time from graft to failure for failed grafts, and to last follow-up for surviving grafts. Loss to follow-up was incorporated into Kaplan-Meier analysis. Variables that were significant in univariate survival analysis were included in multivariate analysis, to calculate adjusted risk factors controlled for potential confounders. A Cox proportional hazards model clustered by patient was chosen. For adequate statistical power, only risk factors with 25 grafts or more in each category were included.¹⁶⁻¹⁷

RESULTS

SURVIVAL OF FIRST PENETRATING GRAFTS FOR KERATOCONUS

Keratoconus was the most common indication for graft in the total cohort of penetrating keratoplasties (**Table 1**). There was a significant difference ($p < 0.001$) in age at graft between patients with first grafts for keratoconus (median 30 years, range 8-88 years) compared with the remaining cohort of penetrating grafts (median 70 years, range 0-99 years). First penetrating grafts for keratoconus exhibited significantly better survival (89% and 49% at 10 and 20 years post-graft, respectively) than did penetrating grafts performed for other indications ($p < 0.001$, **Figure 1**).

Overall, 7% of first penetrating grafts for keratoconus failed over a period of 23 years, in 19% of cases from irreversible immunological rejection (**Table 2**). By comparison, 23% of the total cohort of penetrating grafts failed, 29% of these from rejection. There was a significant difference between the frequency of failed grafts for keratoconus compared with all penetrating grafts ($\chi^2(1) = 473.0$, $p < 0.001$), as well in the frequency of rejected grafts ($\chi^2(1) = 10.7$, $p = 0.001$). Rejection (reversible or irreversible) in first penetrating grafts for keratoconus occurred most frequently in the first year after graft, with 48% of first rejection episodes occurring within 1 year and 90% within 4 years post-graft. Time to rejection ranged from 10 days to 21 years (median 1 year). Rejection was a significant risk factor in graft survival ($p < 0.001$, **Figure 2**). In patients with bilateral grafts, there was no difference in the risk of rejection after the second eye was grafted, if the time between bilateral grafts was more than one year, compared with one year or less (RR=1.02, 95% confidence intervals (CI) 0.63, 1.65, $p = 0.95$). Further, there was no difference in the unadjusted risk of rejection between first and second grafted eyes ($p = 0.19$).

LONG-TERM GRAFT SURVIVAL IN PATIENTS WITH KERATOCONUS

A total of 235 first penetrating grafts for keratoconus (62%) in 215 patients survived 15 years or more (median 17 years). Median recipient age at surgery for these long-surviving grafts was 32 (range 11-77) years, similar to all grafts for keratoconus. Kaplan-Meier survival was 17% (95% CI 2%, 46%) at 23 years. For long-surviving grafts performed for any indication, there was no significant difference in

survival between patients grafted for keratoconus and the remaining cohort ($p=0.36$, **Figure 3**). The most common reasons for graft failure were failure from unspecified cause, astigmatism, rejection and recurrent keratoconus (**Table 2**).

FACTORS ASSOCIATED WITH GRAFT FAILURE OVER TIME: MULTIVARIATE ANALYSIS

Adjusted risk factors for graft failure were determined using a Cox proportional hazards model (**Table 3**). Variables included in the final model were age at graft, geographical location (center), surgeon experience (those performing over 200 grafts), corneal vascularization at graft or post-graft, graft size, refractive surgery post-graft, inflammation in the past or at graft, follow-up arrangements, rejection episodes, uveitis and microbial keratitis or stitch abscess post-graft. Donor age was not found to influence graft survival.

To determine if risk factors for graft survival changed over time, multivariate analysis was performed over the complete follow-up period and at 5 year intervals (**Table 4**). As time post-graft increased, the number of risk factors in each subset decreased. No risk factors for failure were identified for the 39 grafts surviving 20 years or more. After 15 years, the major risk factor for graft survival/failure was the center effect: the worst center had more than 7 times the hazard than the best center.

VISUAL ACUITY IN PENETRATING GRAFTS FOR KERATOCONUS

The proportion of eyes with a first penetrating graft for keratoconus that achieved a BCVA of 20/40 or better was 74% at most recent follow-up compared with 8% pre-operatively (**Figure 4**). Median BCVA pre-operatively was 20/200 (range: no light perception to 20/16), with contact lens intolerance being the reason for transplantation in eyes with good pre-operative BCVA. Median post-operative BCVA at last follow-up was 20/30 (range: no light perception to 20/13). The median change in BCVA after penetrating keratoplasty was an improvement of 6 lines (range: 10 lines worse to 13 lines better). Of eyes with a pre-operative BCVA of 20/20 or better, 63% had worse, 26% had the same, and 11% had better BCVA at the most recent follow-up.

Overall, visual outcomes were significantly different in penetrating grafts performed for

keratoconus, compared with all other penetrating grafts (**Table 5**). Spectacles and/or contact lenses were prescribed for 61% of eyes grafted for keratoconus, compared with 48% in all other penetrating grafts ($\chi^2(1)=130.1$, $p<0.001$). Major astigmatism (≥ 5 diopters) was more prevalent in eyes grafted for keratoconus compared with in all other penetrating grafts ($\chi^2(1)=39.0$, $p<0.001$). At last follow-up, significantly more eyes grafted for keratoconus had achieved a BCVA of 20/40 or better (74% versus 45%, $\chi^2(1)=782.6$, $p<0.001$), and an improvement in BCVA postoperatively ($\chi^2(2)=269.4$, $p<0.001$), compared with all other penetrating grafts.

Since BCVA may stabilize over several years post-graft, the proportion of patients with BCVA of 20/40 or better at last follow-up was plotted for patients over time (**Figure 5**). Smaller numbers at increasing years post-graft caused greater variability in the data. The proportion of eyes with BCVA of 20/40 or better at last follow-up was 70% or above until 11 years post graft, remaining above 59% up to 18 years post-graft. For patients with grafts surviving more than 15 years, BCVA of 20/40 or better at last follow-up was achieved by 142 eyes (63%), while 82 eyes (37%) had BCVA worse than 20/40.

COMMENT

Within a large national multi-center Registry, graft survival for eyes that received a first penetrating graft for keratoconus was significantly better than for the remaining cohort of penetrating grafts, and the proportion of grafts with BCVA of 20/40 or better increased from 8% pre-operatively to 74% at the time of most recent follow-up. Risk factors for failure of grafts for keratoconus over a follow-up period of 23 years were similar to those for all penetrating grafts.¹ The number of risk factors for graft failure decreased with longer graft survival times.

Consistent with many reports over the years,^{1-3, 18} occurrence of rejection episodes in eyes grafted for keratoconus was a significant risk factor for graft failure. While most rejection episodes occurred soon after graft (90% in the first four post-operative years), some still occurred years later, with the longest time to first rejection being 21 years. Malbran and Fernández-Meijide¹⁹ found a higher incidence of rejection if a bilateral graft for keratoconus was performed within one year of the first graft. In contrast, we found the timing of bilateral grafts made no difference to the risk of rejection after the second eye was grafted. We have previously reported that patients with bilateral corneal grafts who suffer a graft rejection episode in one eye were then at significantly greater odds of suffering a rejection episode in the other corneal transplant.²⁰ However, in the current cohort of low-risk patients with first grafts for bilateral keratoconus, there was no significant difference in the unadjusted risk of rejection between first and second grafted eyes.

With respect to graft size, grafts of intermediate diameter appeared to have the best outcomes. Large grafts lie closer to the limbus with its load of recipient antigen presenting cells than do intermediate grafts. The reason for the increased risk of failure of small diameter grafts is unknown. Case load also influenced graft survival significantly: surgeons who had registered more than 200 penetrating keratoplasties achieved significantly better graft survival. Of interest, advanced recipient age (60 years or older at the time of graft), but not donor age, was associated with significantly worse outcome in multivariate analysis. This effect was independent of the occurrence of rejection episodes and cannot have been due to the influence of regrafts in the same eye, given that the analysis was

performed on first grafts in any one eye. Possibly some unidentified factor associated with the length of time older patients have suffered from keratoconus may be responsible for poorer graft survival in these recipients.

While grafts for keratoconus showed better survival rates compared with survival of grafts for other indications for the first 15 post-operative years, after this time graft survival appeared independent of indication for graft. Penetrating grafts in high-risk eyes may be more likely to fail prior to 15 years, whereas all long-surviving grafts may be equally at risk of graft failure from late endothelial cell loss.²¹⁻²⁴ In grafts performed for keratoconus, late graft failures were more often attributed to unspecified causes, recurrent keratoconus¹¹ or astigmatism²⁵ and less often from rejection. For grafts surviving 15 years or more, geographical location (center effect) was a risk factor for failure, with the worst center having more than 7 times the risk of graft failure than the best. Efforts to tease out the basis of the center effect have thus far been unsuccessful. Donor and Eye Bank-related factors do not influence graft survival significantly and we have no evidence to suggest that patient populations with keratoconus differ across different geographic regions. All surgeons contributing data to the Registry do so using an identical proforma. Long-term survival for grafts with normal (rather than impaired) recipient endothelium was estimated by Borderie *et al* to be 41±3% at 20 years, falling to 3±1.0% at 30 years.²⁶ Since the majority of individuals with keratoconus would be expected to have normal recipient endothelium,²³ the 20 year graft survival rate of 49% (95% CI, 40%, 57%) from our study compares well with the predictions of Borderie *et al*.

A major weakness of registry studies is loss to follow-up, which is higher in keratoconus patients than in the remaining cohort. There may be many patients with long-surviving grafts who have not attended a follow-up appointment for years. As patients with a failed graft are likely to seek medical attention, loss to follow-up may lead to an under-estimate of graft survival at longer survival times. Further, as more data are collected by the Registry, especially after 30 years post-graft when long-surviving grafts are more likely to fail, the data may become even more biased towards the reporting of failed grafts, so that the rate of failure is over-estimated.

The principal purpose of corneal transplantation in patients with keratoconus is to improve visual function and reduce disability. In this study, 86% of grafts for keratoconus were performed to improve vision, of which visual acuity is one measure. Visual acuity is difficult to standardize in community practice. Even when meticulously measured, BCVA may not be relevant to the daily functioning of the patient. A contact lens may be tolerated for the short time while BCVA is measured but the patient, especially one with keratoconus, may not be prepared to use the lens with optimal refractive correction at other times. However, despite its limitations, BCVA is adequate to confirm the improvement in vision after penetrating keratoplasty for keratoconus. At the time of most recent follow-up, a BCVA of 20/40 or better was achieved by 74% compared with 8% pre-operatively. However, for eyes with a pre-operative BCVA of 20/20 or better, only 11% showed improved BCVA at last follow-up, possibly because of regression to the mean.²⁸ Patients with good pre-operative BCVA, although less likely to achieve better BCVA post-operatively, may accept a reduction in BCVA as an alternative to wearing a contact lens. Overall, a higher proportion of eyes grafted for keratoconus exhibited a BCVA of 20/40 or better, compared with all penetrating grafts, but this gain was achieved at the expense of a greater need for refractive aids and with significantly worse major astigmatism. Astigmatism is a particular problem with grafts for keratoconus²⁶ and may be a cause of late graft failure.²⁵ In patients with keratoconus, visual acuity may take several years to stabilize post-graft:⁹ in this study, relatively stable visual acuity was not observed until about 5 years after transplantation.

Small single-center case series have reported long-term survival for keratoconus grafts of 85% from 112 eyes¹¹ and 93% from 125 eyes¹³ at 25 years. Registries contain a broader range of data than single-center studies and allow a more complete analysis of the factors that influence graft survival. However, the potential for under-reporting graft survival because of loss to follow-up must be acknowledged. We report that in 4,834 eyes grafted for keratoconus, 10, 20 and 23 year Kaplan-Meier graft survival was 89%, 49% and 17%, respectively. For long-surviving penetrating grafts such as for keratoconus, graft survival from our study and estimated by Borderie *et al*²⁶ suggest that, overall, there is a low probability of graft survival after 30 years. Factors such as surgical skill and experience may increase

graft lifespan: a “best-case” Cox model incorporating the lowest hazard ratios for risk factors such as the center-effect and surgeon case-load, predicted survival rates of 85% and 46% at 20 and 23 years, respectively. Surgeons with the most experience should be favoured when keratoplasty is unavoidable. A young person having a penetrating corneal graft is likely to require repeat keratoplasty in decades to come. Such repeat grafts tend to exhibit shorter survival than the first graft¹⁻², and for young patients, especially those with excellent BCVA, alternatives to surgery are preferable.

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FIGURE LEGENDS

Figure 1. Survival of first penetrating grafts for keratoconus. Kaplan-Meier graft survival plots for first penetrating grafts for keratoconus and for all other penetrating corneal grafts, n represents number at risk. [http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF1%7cL%7ctiff)

[3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF1%7cL%7ctiff](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF1%7cL%7ctiff)

Figure 2. Influence of episodes of rejection on corneal graft survival. Kaplan-Meier plots for first penetrating grafts for keratoconus that have suffered one or more episodes of rejection, compared with those without any episode of rejection, n represents number at risk. [http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF2%7cL%7ctiff)

[3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF2%7cL%7ctiff](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF2%7cL%7ctiff)

Figure 3. Long-term survival of grafts for keratoconus. Kaplan-Meier graft survival plots for first penetrating grafts for keratoconus and for all other penetrating grafts that have survived at least 15 years from the time of graft, n represents number at risk. [http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF3%7cL%7ctiff)

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Figure 4. Visual outcome in first penetrating grafts for keratoconus. BCVA measured with spectacles and/or contact lens, pre-operatively (top panel) and at most recent follow-up (lower panel). CF = count fingers, HM = hand movements, LP = perception of light, NLP = no perception of light.

[http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF4%7cL%7ctiff)

[3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF4%7cL%7ctiff](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF4%7cL%7ctiff)

Figure 5. Proportion of eyes with BCVA of 20/40 or better over time, measured with spectacles and/or contact lens, at year of most recent follow-up. Numbers at each time interval are shown above the data points. [http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF5%7cL%7ctiff)

[3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-](http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?S=BEPBFPJGJOEDDKFMHNCOKHAGCJJPMAA00&Graphic=00000820-201106000-00001%7cFF5%7cL%7ctiff)

[201106000-00001%7cFF5%7cL%7ctiff](#)

Table 1. Indications for penetrating keratoplasty in the Australian Corneal Graft Registry	
Indication	Number (percent)
Keratoconus	4,834 (31%)
Pseudophakic/aphakic bullous keratopathy	3,927 (25%)
Failed previous graft	2,993 (19%)
Corneal dystrophy	1,179 (8%)
Other	2,610 (17%)
Total	15,543 (100%)

Table 2. Reasons for graft failure in all 4,834 grafts for keratoconus and in 235 long-surviving grafts for keratoconus

Reason for graft failure	All grafts for keratoconus Number (percentage^a)	Grafts surviving ≥ 15 years Number (percentage^a)
Rejection	66 (19%)	6 (12%)
Failed graft, unspecified cause	64 (19%)	15 (31%)
Primary graft failure	41 (12%)	0 (0%)
Endothelial cell failure	40 (12%)	4 (8%)
Astigmatism (regular or irregular)	37 (11%)	9 (19%)
Eye injury	27 (8%)	4 (8%)
Recurrent keratoconus	16 (4%)	6 (12%)
Corneal scar/opacity	9 (2%)	5 (10%)
Other ^b	44 (13%)	0 (0%)
Total failed grafts	344 (100%)	49 (100%)
^a Percentage of failed grafts.		
^b Including corneal abscess, perforation, neovascularization and degeneration, glaucoma, endophthalmitis, herpetic keratitis and wound dehiscence.		

Table 3. Multivariate analysis: risk factors for graft failure (n = 4,834)

Risk factor	Category	Hazard ratio (95% CI)^a	P
Geographic location (center)	Centers 1-5	0.79 (0.45, 1.39) to 2.52 (1.62, 3.94)	global <0.001
Case-load >200 grafts	Yes	0.63 (0.49, 0.83)	0.001
Follow-up arrangements	Not by surgeon	0.63 (0.47, 0.84)	0.002
Recipient age at graft	≥ 60 years	2.36 (1.56, 3.57)	<0.001
Graft size	< 7.5 mm or > 8.5 mm	1.61 (1.20, 2.17)	0.002
Neovascularization of graft	Yes	2.11 (1.44, 3.08)	<0.001
Rejection episodes	≥ 1 episode(s)	1.89 (1.45, 2.46)	<0.001
Microbial keratitis in graft	Yes	3.45 (1.99, 6.00)	<0.001
Uveitis post-graft	Yes	2.41 (1.13, 5.11)	0.02

^a Referent hazard ratio in each instance was 1.00; CI, confidence interval.

Table 4. Multivariate analysis: risk factors for graft failure in keratoconic eyes, stratified by graft survival time

Survival (years)	n^a	Risk factor	Category	Hazard ratio (95% CI)^b	P
<5 years	3,241	Recipient age at graft	≥ 60 years	2.15 (1.34, 3.47)	0.002
		Inflammation in eye at graft	Yes	2.60 (1.23, 5.48)	0.01
		Graft size	< 7.5mm or > 8.5mm	1.89 (1.29, 2.75)	0.001
		Episode(s) of graft rejection	≥ 1episode(s)	2.72 (1.97, 3.76)	< 0.001
		Neovascularization of graft	Yes	2.44 (1.62, 3.69)	< 0.001
		Microbial keratitis post-graft	Yes	2.18 (1.07, 4.43)	0.03
		Refractive surgery post-graft	Yes	0.43 (0.24, 0.77)	0.005
		Follow-up arrangement	Not by surgeon	0.45 (0.29, 0.70)	< 0.001
		≥5 - <10 years	970	Recipient age at graft	≥ 60 years
Corneal vascularization at graft	Yes			2.80 (1.31, 5.97)	0.008
≥10 - <15 years	388	Episode(s) of graft rejection	Yes	2.03 (1.10, 3.75)	0.02
≥15 years	235	Geographic location (center)	Center 1-5	1.0 to 7.60 (2.72, 21.2)	< 0.001

^a n = number of first penetrating grafts performed for keratoconus.

^b The alternative for each risk factor is the reference category, with a hazard ratio of 1.00; CI, confidence interval.

Table 5. Visual correction, major astigmatism and change in visual acuity at last follow-up for keratoconus eyes and all other penetrating grafts

Characteristic	Grafts for keratoconus Number (percent)	Other penetrating grafts Number (percent)
<i>Type of visual correction:</i>		
spectacles	2,135 (44%)	6,459 (42%)
contact lens	614 (13%)	827 (5%)
spectacles and contact lens	142 (3%)	213 (1%)
none	1,943 (39%)	8,044 (52%)
<i>Major astigmatism in graft:</i>		
< 5 diopters	3,704 (77%)	12,709 (82%)
≥ 5 diopters	1,129 (23%)	2,830 (18%)
<i>BCVA at last follow-up:</i>		
better or equal to 20/40	3,278 (74%)	6,351 (45%)
worse than 20/40	1,156 (26%)	7,840 (55%)
<i>Change in BCVA after graft:^a</i>		
no change	163 (5%)	1,363 (13%)
better	3,088 (88%)	7,599 (73%)
worse	236 (7%)	1,433 (14%)

^a Measured at most recent follow-up.