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Risk factors for graft failure after penetrating keratoplasty

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Abstract

The objective of our study was to define principal risk factors for graft failure in patients who underwent penetrating keratoplasty (PK).

Retrospective data obtained from a cohort of 895 penetrating keratoplasties performed between 2001 and 2006 were analysed. Recipient related factors, graft characteristics, and surgical technique were assessed in a univariate analysis and with a multivariate proportional hazard model to detect principal risk factors for definitive graft failure.

Multivariate analysis showed clear significance for diagnosis and number of previous grafts and border line significance for the oldest donor age group. Patients with keratoconus had the best 10-year survival estimate (95%), followed by endothelial and stromal dystrophies (both 55%), infectious leukomas (49%), trauma (33%) and chemical burns (14%). Primary PK grafts had a survival rate of 81%, second grafts of 33% and third or more grafts of 16%. Overall 10-year survival estimate based on univariate analysis was found to be 65%.

In conclusion, we found that primary diagnosis and previous graft failures in the recipient are the most important risk factors of graft failure after a PK.

Abbreviations: HLA = human leukocyte antigen, PK = penetrating keratoplasty.

Keywords: cornea, graft failure, multivariate analysis, penetrating keratoplasty, risk factors

1. Introduction

Penetrating keratoplasty (PK) is a 110-year-old procedure whose effectiveness and safety has led to be the most frequently performed type of transplant worldwide. Even with the consolidation of new, less invasive, lamellar techniques, in 2012 PK still accounted for about 70% of corneal transplantations.[1]

The corneal transplant, the oldest of all, is indicated in those diseases that damage the original cornea, making it opaque, with the consequent loss of vision (infections, traumatisms, burns, etc.). The first corneal transplant in our country was carried out in 1940 at the Centro de Oftalmologia Barraquer in Barcelona. Nowadays, in Spain there are 180 accredited hospitals to perform this type of transplant and 112 centres authorized to obtain corneas, distributed throughout the Autonomous Communities in Spain. During 2016 there were 3862 donors of which 7511 corneas were obtained. A total of 4187 transplants were performed, continuing the upward trend of the previous year. Of the 7511 corneas obtained, 34% (2577) were rejected, 31% (794) due to donor problems and 69% (1783) during processing.[2]

This type of transplant differs in that the cornea is an avascular tissue with blood supply only at the limbus and it is immunologically privileged which makes it different from other transplanted organs and therefore has a much lower rejection rate. Several recent studies on PK outcomes focused on specific indications, such as Fuchs's dystrophy and pseudophakic corneal edema[3–5] or focused on endothelial cell loss.[6] In our study, we aim to identify both donor and recipient principal risk factors for PK failure, based on graft survival estimates and considering all indications for PK. Similar global studies date back to the 1990s.[7] Our analysis includes univariate as well as multivariate techniques. We consider recent recommendations for transparent reporting of a multivariable prediction model for individual prognosis and diagnosis (TRIPOD).[8] This includes careful and methodical estimation of sample size for avoiding over fitting effects and an accurate data management through multiple imputation and pooling handling of missing values.

2. Materials and methods

2.1. Study protocol

Clinical records of all patients who underwent a penetrating keratoplasty due to any cause at the Centro de Oftalmologia Barraquer between 2001 and 2006 were considered for our retrospective cohort study (n = 966). Cases with missing primary diagnosis were excluded (n = 42). Children aged 11 years old or below were also excluded (n = 23) because the cumbersome examinations may lead to the possibility of misdiagnosing the outcome of interest.[9,10] Furthermore, we excluded 6 cases with donor age below 21 years because the cornea in children is not fully developed and such donations are a rare exception at our eye bank,

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with the large majority of donations between age 50 and 90 years. This resulted in a final number of 895 cases to be analysed. All donor corneas were obtained from enucleated eyes and were provided by the Banco de Ojos para Tratamientos de la Ceguera, Barcelona. Ethical approval is currently not required in Spain for retrospective studies which are based only on reviews of clinical records.

After surgical intervention, all patients received a corticoid-based therapy for preventing early graft rejection. However, the dosage of anti-inflammatory medications or the prescription of additional therapies such as antibiotics or immunosuppressants depended on the background and clinical status of each patient. Donor cornea endothelial cells density lower limit was 2200 cell/mm^2.

Outcome of interest was graft failure, defined as the loss of graft transparency capable of compromising vision for at least 3 months despite maximum anti-inflammatory therapy. For declaring a graft failure, photographical or written description of the affected graft was checked in the clinical history. If during the follow-up an eye lost its visual acuity because of another reason but the graft was still transparent, it was not being considered as a failure. Graft failure assessment was made in each clinical consultation by a corneal surgeon or general ophthalmologist. Frequency of consultation was not standardized but at least 1 consultation every year had been performed.

2.2. Variables

Twelve variables were extracted for each patient to develop the model. This selection was made according to convincing or probable risk factors identified in previous studies.[7,11,12] Recipient related variables considered were sex, age, primary indication/diagnosis for PK, vascularization of corneal bed and number of previous PK performed. Graft-related variables were donor's age and sex, preservation status of the graft, time from donor's death to enucleation and from donor's death to transplantation. Graft diameter and the presence or not of a combined surgery were considered as surgery technique related variables.

Continuous variables (age of the donor, age of the recipient, time from death to enucleation, and time from death to transplant) were categorized in discrete intervals. Cutting points for categorization of continuous variables were selected based on clinical expertise and previous studies regarding various donor and receipt characteristics that lead to an increased risk of graft failure.[13]

2.3. Statistical methods

2.3.1. Survival. Considering previous prognostic studies, the survival rate of penetrating keratoplasty at 5 and 10 years is around 74% and 63%, respectively.[7,12] In order to avoid the effect of overfitting,[14,15] we estimated a sample size of 900 to 1000 cases (around 240 failures) in order to achieve an event per variable ratio of 20 to 30.

Data were censored at the time of the last visit if there was no failure event. Association of recipient, graft, and surgical technique factors with the occurrence of a failure event were assessed in univariate and multivariate proportional hazards models.

2.3.2. Univariate. A starting unadjusted univariate analysis was performed using Kaplan Meier statistics and log rank tests (log rank test for trend when relevant), identifying statistically significant differences ($P < .05$) between individual subgroups. Life table analysis was used to compute the 10-year survival estimates of the graft.

2.3.3. Multivariate. Then, Cox proportional hazards regression model and pooling of imputed data were performed by a forced entry method of all variables. Multiple imputation method[16,17] addressed to fulfil missing data of predictors. Around 6 out of the 12 studied variables were included in the multiple imputation model. Five imputed data sets were created as part of multiple imputation, and then combined to produce an overall estimate of each regression coefficient. Sparse categories of nominal variables, such as diagnosis or type of combined surgery, were grouped into a single "other" category.

All analyses were made using IBM SPSS Statistics 22 software.

3. Results

Altogether 895 PK from 778 patients were included in the study. Mean follow-up time was 5.8 years. Among these cases, 29% (n = 258) were identified as a graft failure. Overall 10-year survival estimate based on univariate analysis was found to be 65%.

3.1. Recipient related factors

Univariate analysis revealed a significant influence related to primary diagnosis, number of previous grafts and vascularisation. Recipient sex showed no significant influence (Table 1).

Table 1

Summary of results from univariate analysis (Kaplan–Meier) and multivariate proportional hazard model (Cox regression).

	Missing data	Kaplan–Meier Log rank test*	Kaplan–Meier Log rank test for trend†	Cox regression
Diagnosis	0	**<.001**		**Keratoconus against all others P < *.001***
Recipient age	0	**<.001**	**<.001**	Not significant
Recipient sex	0	.688		Not significant
Vascularisation	23 (2.6%)	**<.001**	**<.001**	Not significant
Number previous grafts	0	**<.001**	**<.001**	**First against all others P <*.001***
Donor age	0	.519	.220	**>80 against 61–80 P =*.043***
Donor sex	2 (0.2%)	.365		Not significant
Preservation	91 (10.2%)	**.001**		Not significant
Time death enucleation	125 (14.0%)	.415	.186	Not significant
Time death transplant	61 (6.8%)	**.003**	**<.001**	Not significant
Graft diameter	3 (0.3%)	**.013**	.304	Not significant
Combined surgery	0	**<.001**		Not significant

Total number of cases n = 895.

* The log rank test gives equal weights to the contribution of each failure time.

† Tests the probability that there is a trend in survival scores across the groups.

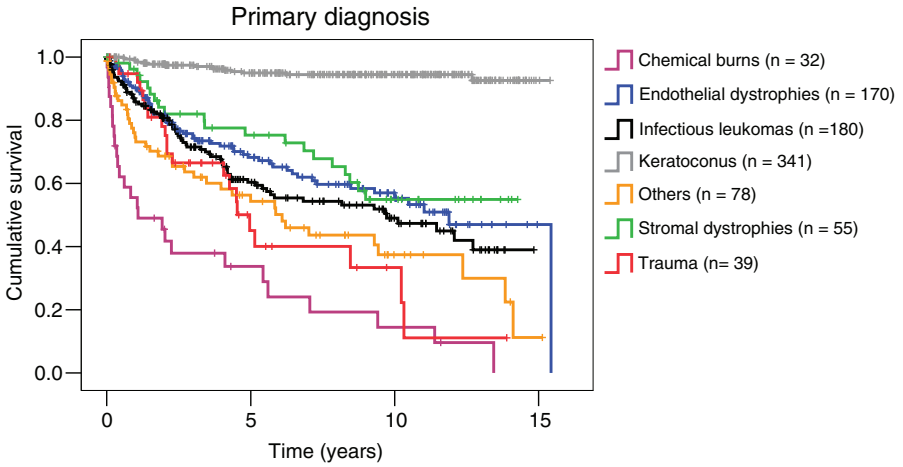

Figure 1. Kaplan–Meier plots of graft survival in patients with different primary diagnoses. The 10-years estimates showed the difference of prognosis between keratoconus and other procedures. Keratoconus was also the most frequent diagnosis (n=341), followed by infectious leukomas (n=180) and endothelial dystrophies (n=170).

Considering primary diagnosis, patients with keratoconus showed the best 10-year survival estimate (95%), followed by endothelial and stromal dystrophies (both 55%), infectious leukomas (49%), trauma (33%), and chemical burns (14%); other diagnoses resulted in a 10-year survival rate of 37% (Fig. 1).

Primary PK grafts had the best 10-year survival estimate (81%), followed by second grafts (33%) and third or more grafts (16%). Avascular recipient corneas had the best 10-year survival estimate (74%), followed by vascularisation in 1 to 3 quadrants (37%) and vascularisation in all 4 quadrants (28%). Recipient with age younger than 50 years showed 10-year survival estimate between 83% and 73%, which compared to estimates between 47% and 44% for recipients older than 50 years (Table 1, Fig. 2).

Multivariate analysis for recipient related factors showed significant results only for primary diagnosis and number of previous grafts. Compared with keratoconus, stromal dystrophies and endothelial dystrophies showed a mean hazard ratio of failure of 4.6 and 6.0, respectively, followed by infectious leukomas (7.4), trauma (10.0), and chemical burn (11.9); other diagnoses resulted to have a mean hazard ratio of 9.5, compared with keratoconus. Second grafts had 2.6 times and third and subsequent grafts 3.8 times higher risk of failure (Table 1, Fig. 3).

3.2. Graft characteristics. Considering univariate analysis, preservation status and time between death and transplant showed a significant effect for PK (Table 1). No preserved corneas showed a 10-year survival estimate of 71% as compared to preserved corneas with 56% (Fig. 4), whereas time between death and transplant of <24 hours between 73% and 70%, a time between 24 and 36 hours of 61%, and more than 36 hours of 52%, all estimates at 10 years post PK (graph not shown). Donor age, donor sex, and time between death and enucleation showed no significant influence (Table 1). The *P* value for donor sex was just at the limit with.05 after rounding to 2 digits (Fig. 3).

Multivariate analysis showed border line significance ($P = .043$) for one donor age group. Preservation status was just not significant ($P = .096$) and time between death and enucleation and time between death and transplant had clearly no significant influence (Table 1, Fig. 3).

3.3. Surgical technique. Both graft diameter and effect of combined surgery were significant in univariate analysis (Table 1). Graft diameter between 7.0 and 7.4 mm as well as between 8.0 and 8.4 mm showed the best 10-years survival estimate (70% and 69%), followed by diameters of 7.5 to 7.9 mm (60%) (Fig. 4). No combined surgery resulted in a 10-year survival estimate of 67% and a combination with vitrectomy displayed 26%. The combination with other surgeries (like, for instance, Flieringa ring implantation or cataract surgery) it was 61% (graph not shown). However, multivariate analysis revealed no-significance for graft diameter and combined surgery (Table 1, Fig. 3).

4. Discussion

Correlation between the different analysed characteristics is a foreseeable event capable of leading to confusion biases in univariate analysis. For example, eyes with chemical burns or trauma were more likely than keratoconus to have vascularization in one or more quadrants. With the goal of identifying independent risk factors, multivariate analysis with Cox proportional hazard regression was performed. Figure 3 shows 4 forest plots that summarize the results found on this approach using multiple imputation combined dataset. Table 1 further, compares the statistically and non-statistically significant differences between the results of the multivariate and univariate analysis.

Our study was of retrospective nature with different follow-up times and possible differential loss to follow-up which might have introduced bias. Data had to be obtained from clinical records, relying on photographic and written descriptions. Another limitation might be the grouping of diagnoses and the different sizes of these diagnosis groups. Primary diagnoses like keratoconus or infectious leukomas were overrepresented in comparison to others like chemical burns or trauma. We have tried to find a balance between grouping of similar diagnoses and the size of these groups. All of the about 1000 cases considered were done in a single center by 6 different surgeons, following the same techniques with the same instruments. Data collection had been standardized with clear guidelines

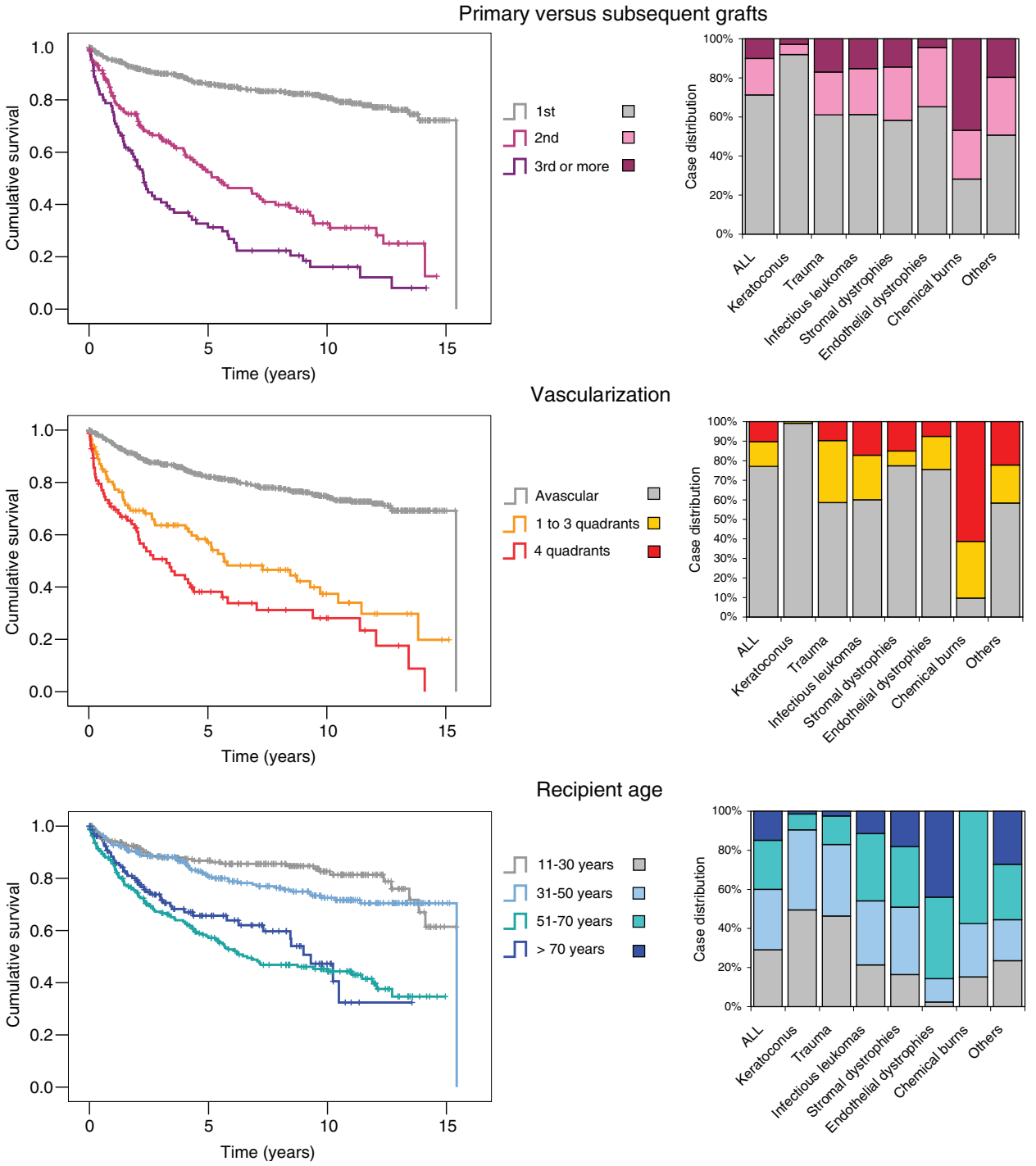

Figure 2. Kaplan–Meier plots of graft survival in patients segmented by number of previous PK, quadrants of vascularization and recipient's age. Stacked bar charts of each one of these variables segmented by diagnosis are also displayed. PK = penetrating keratoplasty.

and some training, but was done by 20 different ophthalmologist, which may have introduced some variations, for instance with respect to the decision on the exact time point of graft failure.

We had performed a similar study with univariate analysis of 2886 cases of PK at our clinic between 1956 and 1987.[11,18] We will refer to this as "our previous study" in the following discussion.

4.1. Diagnosis as principal risk factor for graft failure

The principal aim of this study was to assess independent risk factors for graft failure in PK. Our overall estimated graft failure rate from all causes after a 10 years follow-up was 35%. This value is consistent with previous studies with similar populations and evaluation times which found 40% at 10 years follow-up.[19] In our previous study, we had a total overall graft failure rate of

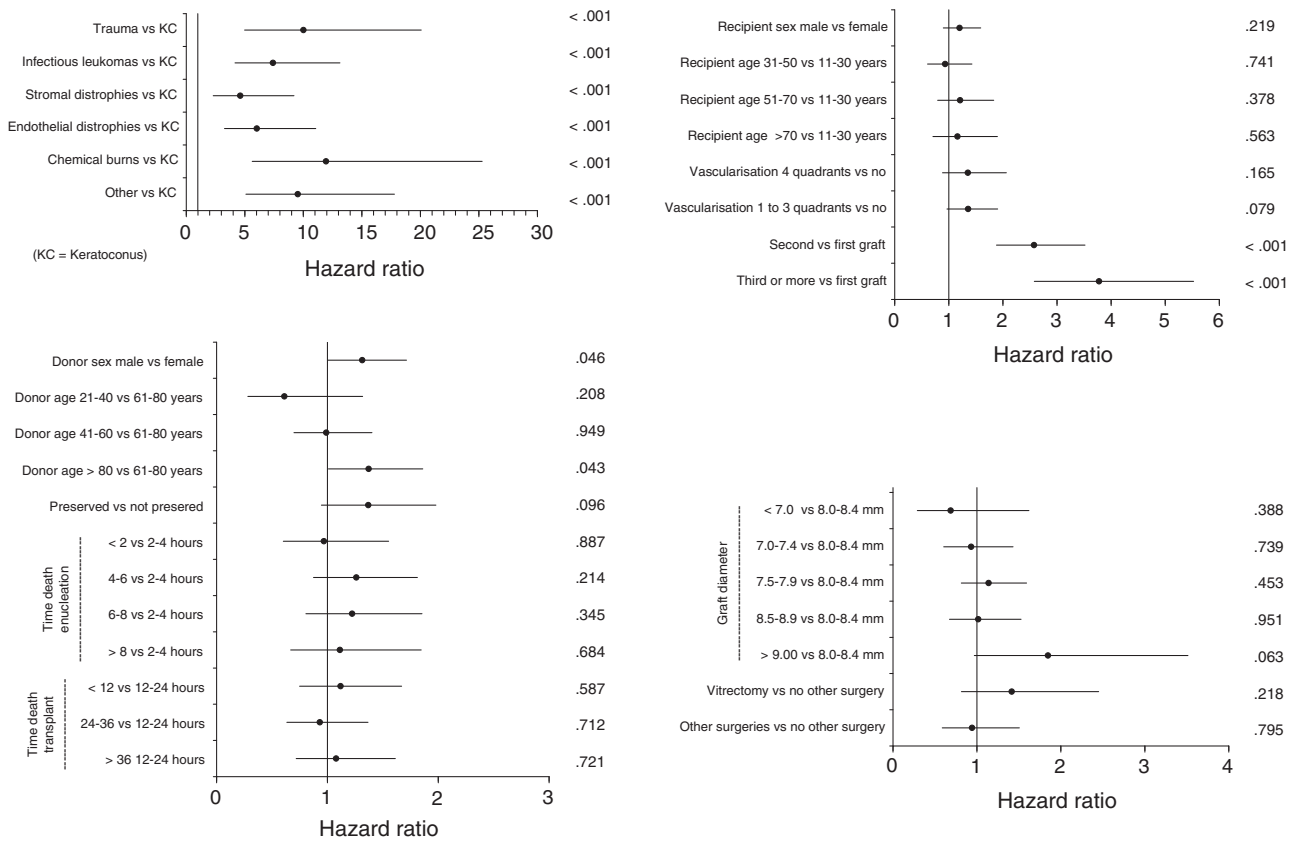

Figure 3. Forest plots displaying multivariate analysis and hazard ratios associated with PK failure. Hazard ratios larger than one indicate a higher risk of graft failure. PK = penetrating keratoplasty.

35% at 5 years follow-up, which compares to 26% in our present study, which is a substantial clincally relavant improvement.

Among all 12 studied variables considered to be potential risk factors for definitive rejection, primary diagnosis other than keratoconus was shown as the strongest predictor in multivariate analysis. Our data reveals in fact, that the graft survival in PK for keratoconus is 95% at 10 years. Very similar keratoconus survival rates (94% and 100%) at 10 years have been reported by several researchers.[20,21] A plausible explanation for this result could be the status of recipient's corneal endothelial cells, which conserve their integrity even in severe cases of keratoconus. It is possible that peripheral endothelial cells maintained after a standard PK procedure contribute significantly to the long-term maintenance of the graft. Considering only our 314 cases with keratoconus, the significance of our evaluated factors with univariate analysis were similar to the results for all diagnoses together, except for preservation type and graft diameter which were not significant for this subgroup. This was in agreement

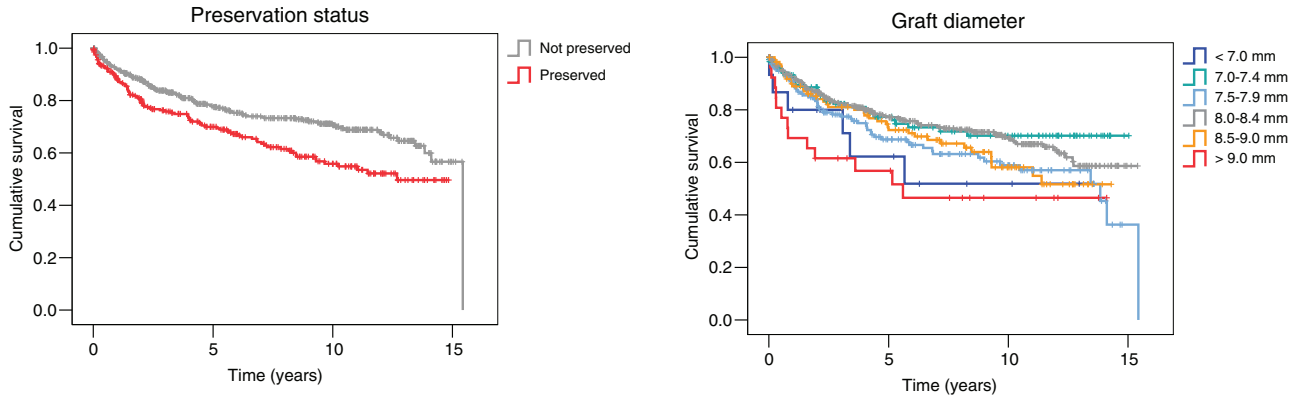

Figure 4. Kaplan–Meier plots and 10-years PK survival estimates in patients with different graft diameters and preservation status of corneal button. PK = penetrating keratoplasty.

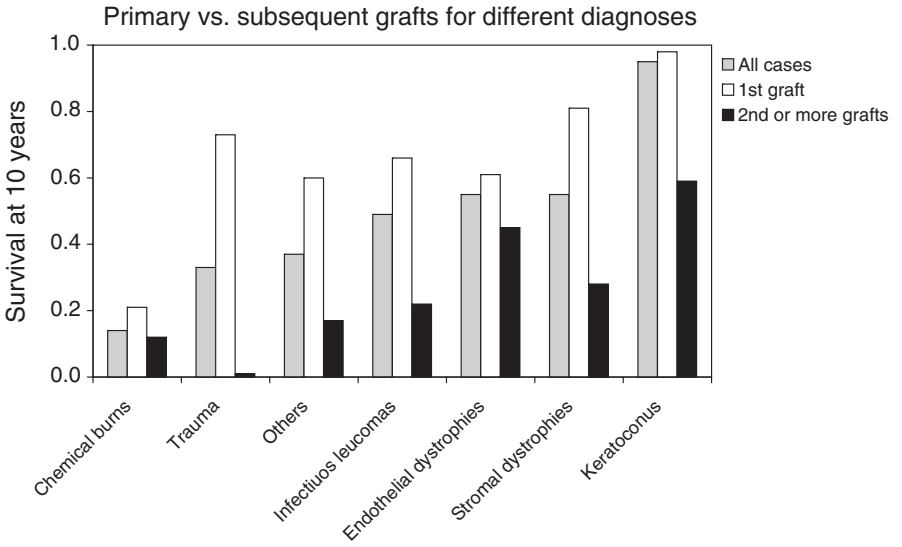

Figure 5. Estimated survival at 10 years after PK for different diagnoses comparing primary versus second or more grafts.

with our multivariate analysis (Table 1). The relative effect on graft survival for first, second, third and more grafts was similar for keratoconus as compared to all diagnoses together, just with a higher percentages of survival due to the overall better prognosis for keratoconus.

For the infectious leukoma category, we found a failure rate of 51% as 10-year survival estimate. We have to consider that this category combined corneal ulcers with different infectious aetiologies which in most cases are not known at the time of the PK surgery. Out of our 180 cases in this category, 35 were caused by herpes simplex virus, 2 by trachoma and for all other cases were nonspecified infectious leukomas. Different types of keratitis may have a specific influence on long term prognosis of PK. For example, herpes simplex keratitis may cause a higher rate of graft failure due a higher risk of corneal neovascularization and the risk of recurrence of the herpetic disease in the graft.[22,23] Trauma and chemical burns related PK deserves also a special mention, since they proved to be the indications with the worst prognosis; 10-year survival rates of 33% and 14% and failure hazard ratios of 10.0 and 11.9 respectively. This makes PK a merely short term, temporary solution to the underlying disease.

Results with regard to primary diagnosis in the present study were very similar to our previous study, except for chemical burn, which was 16% in our previous study and 34% in our present study at 5 years follow-up.

4.2. Influence of a repeated keratoplasty in graft prognosis

As expected in accordance with our previous and other studies[11,18,24–26], repeated keratoplasties demonstrated a poorer prognosis that initial keratoplasty, with a clear increasing trend of risk in both univariate and multivariate analysis. This is probably due to deteriorated condition of the corneal bed, probability of increased intraocular pressure during previous keratoplasty, and the violation of anterior chamber immunological privilege in patients with more than one PK procedure.[27] Evaluating first grafts and second or more grafts separately, the significance of our evaluated factors with univariate analysis was similar to the results for all cases together, however, preservation type and graft diameter were not significant. The 10 year survival for chemical burns and endothelial dystrophies were similar after first grafts compared to second or more grafts. All other diagnoses showed a large difference between first and second or more grafts (Fig. 5). As could have been expected, 10 year survival after second or more grafts was independent of vascularization before the first PK. Recipient age had less impact on second or more grafts when compared to first grafts.

4.3. Neovascularization. A larger meta-analysis, combining studies with univariate or multivariate analysis or both found a significant graft failure increase associated with the number of corneal quadrants affected by neovascularization before PK.[28] This meta-analysis showed that the loss of corneal angiogenic privilege after PK increases the risk of graft failure, becoming and independent risk factor of poor prognosis outcome of penetrating keratoplasty procedures. There is evidence suggesting that the use of antiangiogenic pharmacologic agents such as Bevacizumab may be able to improve survival on high risk neovascularized corneas if used prior to the PK.[29] Our univariate analysis was also significant with respect to neovacularization, but not our multivariate analysis (Table 1). We think that the significant result in our univariate analysis is due to the strong relation between certain primary diagnoses and neovascularization in the present study. As can be seen in Figure 2, diagnosis like keratoconus have minimal corneal neovascularization presence before PK, while chemical burns or trauma were more likely to have vascularization in one or more quadrants.

4.4. Donor age and sex. Donor age was not significant with univariate analysis and showed borderline results with multivariate analysis. Grafts from donors aged 80 years and older were at a slightly higher risk of failure in comparison to patients under 80 years.

The Cornea Donor Study (Mannis 2013) found evidence of a donor age effect at the extremes of the age range. The success rate was higher for donors from 12 to 33 years (96%) and lower for donors from 72 to 75 years (62%); the study did not included donors older than 75 years. The Australian Corneal Graft

Registry reported no significant association of donor age with failure; considering donors up to 97 years of age.[19]

Donor sex revealed no statistical significant results, both with univariate and multivariate analysis, although our multivariate results were near our significance limit of .05 after rounding to two digits. The literature is also not consistent in this respect with confliction results.[3,28,30,31]

Some studies suggest that male grafts can be subject to alloimmune reactivity in female recipients as antigens of the Y genes are only expressed in males and not in females.[32,33] However, earlier investigations on human penetrating keratoplasty did not demonstrate any effect of gender matching.[34] The Collaborative Corneal Transplant Study showed that matching for human leukocyte antigen (HLA): HLA-A, -B and -DR had no significant effect on overall graft survival, the incidence of irreversible rejection or the incidence of rejection episodes.[35] In our study we found a very small tendency of a lower 10 year survival estimate for male donor to female recipients (62%) as compared to the other three matching options (65 to 66%), but far from being statistically significant ($P = .758$; log rank test for Kaplan–Meier analysis).

4.5. Eye banking practices. Factors associated with eye banking practices, including preservation status, time between death and enucleation (considering 12 hours the upper limit) and death to transplant time, were not significant with multivariate analysis. We can find similar outcomes in the bibliography, where retrieval of the donor cornea after brain-death or cardiac-death, death to enucleation time (within standard limits), type of corneal storage medium used within the eye bank, or death to graft time (within approved limits for the preservation medium used) did not influence corneal graft survival significantly.[19] None of the factors related to the processing of the tissues (post-mortem interval, length of storage and endothelial cell density) were associated with any increased risk of graft failure in Cornea Donor Study[36] neither for the results from the Veneto Eye Bank.[37]

4.6. The graft diameter influence

Large diameter penetrating keratoplasties are evaded due to closeness of limbar vasculature because the proximity to conjunctival vessels and therefore to antigenic material.[38] In our present study, statistically significant differences were found when comparing graft diameters in univariate, but not with multivariate analysis. Larger than 9 mm grafts had the lowest 10 years survival estimate and were just not significant compared with 8.0 to 8.4 mm grafts ($P = .063$). The literature has varied conclusions with studies reporting no association between graft size and the incidence of allograft rejection and lower allograft rejection rates with larger[39] or smaller[40] graft sizes. Bidaut-Garnier et al[41] found a no significant difference in graft diameter, dividing the sample in < 8 mm or > 8 mm.

4.7. Controversy about combined surgery procedures

Unlike the proved evidence regarding the association between repeated PK and an increased risk of graft failure, combined keratoplasty with pars plana vitrectomy (PPV) or other surgeries remains controversial.[24,42] Fasolo et al[37] showed a 2.8-fold greater risk of graft failure after PK and PPV, however Sugar et al[42] and Yu et al[43] did not find an increased risk of graft failure after combined procedures. In our present study, neither vitrectomy PPV nor other surgeries had influence in the risk of graft failure in multivariate analysis but PPV did in univariate analysis. A possible explanation for this could be explained because of the low number of combined surgeries in our sample and the strong interdependency between PK-PPV procedure and patients with trauma as primary diagnosis (who had a worse prognosis than other diagnoses).

In summary, long term prognosis of PK depends mostly on the primary diagnosis and the number of previous graft failures in the recipient. Patients with keratoconus had the best 10-year survival estimate (95%), followed by endothelial and stromal dystrophies (both 55%), infectious leukomas (49%), trauma (33%) and chemical burns (14%). Primary PK grafts had a survival rate of 81%, second grafts of 33% and third or more grafts of 16%.

In conclusion, our study could not confirm that corneal neovascularization in itself is a risk factor for corneal transplantation as it appeared in other studies. We confirmed that penetrating keratoplasty survival and long-term prognosis is strongly diagnosis related. This could have implications for future patient selection, taking into account another therapeutic or surgical approaches in those cases where the prognosis is worse. Future research should be prospective with fixed follow-up times, balanced grouping of the different diagnoses and include lamellar procedures of corneal transplants.

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