Donor age as a predictor of cornea transplant success

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ABSTRACT • RÉSUMÉ

Background: The purpose of this study was to examine the association between donor age and cornea transplant success.

Methods: This retrospective cohort study comprised 116 patients who had cornea transplants performed for the first time. The primary analysis was performed to evaluate the time to graft failure as a function of donor age. Donor age was divided into 3 categories: (1) continuous, (2) younger than 65 versus 65 years and older, and (3) younger than 60 versus older than 70 years. We controlled for other variables that may affect graft outcome by multivariate modeling. The primary outcome was graft failure.

Results: No statistically significant association was found between time to failure and donor age [adjusted hazard ratio: 1.004 (p = 0.68) for continuous age, 1.18 (p = 0.68) for age < 65 vs. ≥ 65 years, and 2.10 (p = 0.089) for age < 60 vs. > 70 years]. However, with all model-building strategies, our results demonstrated that all hazard ratios calculated were greater than 1.00 for the older versus the younger aged groups.

Interpretation: The influence of donor age on success of cornea transplants remains unresolved. Large, multicentre prospective cohort studies and randomized trials are needed to decisively determine the impact of donor age on cornea transplant success.

Contexte : La présente étude a pour objet de définir l'association entre l'âge du donateur et la réussite de la greffe de la cornée.

Méthodes : Cette étude rétrospective comprenait une cohorte de 116 patients qui avaient subi une première greffe de la cornée. L'analyse primaire cherchait d'abord à évaluer le moment de l'échec de la greffe en fonction de l'âge du donateur. L'on a réparti cet âge en 3 catégories : (1) l'âge continu, (2) les moins de 65 versus les plus de 65 ans, et (3) les moins de 60 versus les plus de 70 ans. Des modélisations à variables multiples nous ont permis de vérifier d'autres variables qui pouvaient affecter le résultat de la greffe. Le résultat principal a porté sur l'échec de la greffe.

Résultats : Aucune association statistiquement significative n'a été trouvée entre le moment de l'échec et l'âge du donateur [risque relatif rajusté : 1,004 (p = 0,68) pour l'âge continu, 1,18 (p = 0,68) pour l'âge < 65 vs. ≥ 65 ans, et 2,10 (p = 0,089) pour l'âge < 60 vs. > 70 ans]. Toutefois, compte tenu de toutes les stratégies de

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modélisation, nos résultats démontrent que tous les risques relatifs calculés dépassent 1,00 chez les groupes âgés versus les jeunes.

Interprétation : L'influence de l'âge du donateur sur la réussite de la greffe de la cornée demeure une question non résolue. Il faut poursuivre des études de cohortes prospectives, multicentriques et randomisées, pour établir définitivement l'impact de l'âge du donateur sur la réussite de la greffe de la cornée.

The rate of corneal graft survival is variable, with reasonable estimates of 2- and 5-year graft survival rates being 78.8% and 64.5%, respectively.[1] There are many factors thought to play a role in graft survival,[2–7] and these include patient age, sex, history of glaucoma, preoperative diagnosis, corneal vascularization, graft size, and cause of donor death. Other possible factors include donor age, postmortem time, and storage time.

The question of whether or not donor age affects the success of cornea transplantation is of considerable importance, and will become more so in coming years as the population ages. The aging of the "baby boom" generation potentially holds significant consequences for the health care system. One of the repercussions in the field of cornea transplantation will be that the average age of corneas available for transplant will increase, as the average age of cornea donors is likely to rise. Increasing numbers of young people deemed unsuitable for donation because of a history of refractive corneal surgery may also accentuate the situation.

The scientific literature is conflicting and inconclusive about the effect of donor age on survival of transplanted corneal tissue. Several studies seem to support the hypothesis that older tissue performs as well as younger tissue when other important covariates are controlled for,[2,4,8,9] while other studies suggest an association between donor age and graft survival.[10–13]

Corneal tissue is currently in high demand, with the supply becoming increasingly limited due to aging of the population and the use of refractive surgery by prospective donors. Consequently, the relationship between donor age and transplant outcome is one of the most important questions in cornea transplantation today.

Methods

This was a retrospective cohort study, using information from patients' medical records. All patients from one practice (W.H.) who underwent penetrating keratoplasty for the first time at the Ottawa Hospital's General campus or the Children's Hospital of Eastern Ontario between 1995 and 2002 were included in the study. All corneas transplanted in this study were provided by the Ontario Eye Bank, which adheres to quality standards and any evolving changes to those standards set by the Eye Bank Association of America. This ensured a common standard of quality and common criteria for donor corneas. Preoperative treatment was performed in patients with a known history of *Herpes simplex* ocular disease. Treatment included 400 mg of prophylactic oral acyclovir twice a day for 2 weeks prior to surgery and continued use until 9 months after surgery.[14] All patients were given intravenous acetazolamide for half an hour before the procedure to decrease the abrupt change in intraocular pressure that occurs when the eye is opened. All procedures were performed using a retrobulbar block. Patients were mildly sedated with intravenous medazolam with the exception of the pediatric cases, which were done under general anaesthetic. Trephine and donor sizes were dependent on the pathologic condition. If any synechiae were present, synechiolysis was carried out using visoelastic materials and an iris spatula. Anterior vitrectomy was performed whenever vitreous was present in the anterior chamber. Exchange of intraocular lens (IOL) was carried out when there was anterior chamber non-Kelman IOL or decentered Kelman IOL. Suturing technique was either 16 interrupted, or 8 interrupted and 16 continuous 10-0 nylon; interrupted sutures were used in any case with a vascularized cornea. At the end of each case, subconjunctival injection of cefazolin and solumedrol was administered.

Postoperative management usually included topical prednisolone acetate 1% eye drops 4 times a day to every 2 hours, which was adjusted depending on the patient's inflammatory response and intraocular pressure, and a topical fluoroquinolone 4 times a day, which was used for 2 to 3 weeks depending on the epithelial healing response. Follow-up visits were scheduled at 1 day, 1 week, 2 weeks, once every 2 weeks for 2 months, once every month for 6 months,

then once every 2 months for 1 year and every 6 months thereafter.

The primary outcome measured was the time to graft failure. Graft failure was defined by either an episode of corneal edema lasting more than 12 weeks, or by a need to regraft for any reason. The maximum follow-up time allowed was 5 years. The primary predictor was donor age, which was divided into 3 a priori categories for the purpose of the analysis: continuous age, younger than 65 or 65 years and older, and younger than 60 or older than 70 years. The final categorical classification was chosen because the effect of a continuous variable such as age is unmasked when more extreme differences are compared.

Other variables measured that may have an influence on cornea transplant success included the following:

Recipient variables

(1) recipient age
(2) preoperative diagnosis
(3) preoperative *Herpes simplex* infection, which was defined as any history of herpes simplex epithelial keratitis, stromal keratitis, or uveitis that required antiviral treatment
(4) preoperative *Herpes zoster* infection, which was defined as any known history of *Herpes zoster ophthalmicus* with corneal signs such as punctate keratitis, mucous plaque keratitis, stromal keratitis, or uveitis
(5) preoperative visual acuity, which was an indicator of the severity of the disease. The logarithm of the minimum angle of resolution (logMAR) visual acuity for every patient was calculated. We also separated the patients into 2 Snellen groups for analysis, either ≤ 20/200 vs. > 20/200.
(6) preoperative glaucoma, which was defined as any patient who was taking any glaucoma medications preoperatively, or who had previous argon laser trabeculoplasty, trabeculectomy, or valve surgery
(7) preoperative lens status
(8) graft size
(9) presence of synechiae, which was defined as any synechiae noted during surgery that required synechiolysis
(10) anterior vitrectomy, which was defined as any patient who had vitrectomy combined with cornea transplantation
(11) intraoperative complication
(12) postoperative glaucoma, which was defined as any increase in intraocular pressure after surgery that necessitated glaucoma medications, trabeculectomy, or valve surgery

Donor variables

(1) cause of donor death
(2) time from death to corneal harvest
(3) time lapse between storage and transplantation

The Cox proportional hazard model was used to study the donor age–time to graft failure association. This model takes into account graft success or failure, as well as length of time the patient was followed. A patient who developed graft failure was defined as such in the analysis; patients who did not develop graft failure, however, were censored if they were lost to follow-up or were not followed for the maximum period.

All predictors of cornea graft success were first analyzed in a bivariate survival analysis with only 1 predictor and 1 outcome. Kaplan–Meier curves were generated for the bivariate analysis of donor age–transplant failure. All predictors with a p value less than 0.10 were used in the final multivariate model. Three final models were designed for the different categorizations of donor age, namely, continuous donor age, younger than 65 versus 65 years and older, and younger than 60 versus older than 70 years.

The model-building strategy was performed using backward manual model building and the log likelihood test for model choices. Cox–Snell residuals were used to assess the overall model fit.[15] The test of proportionality was performed based on the generalization of Grambsch and Therneau.[16]

The research ethics board of the Ottawa Hospital approved the protocol and execution of this study.

Results

There were 116 patients who met the inclusion criteria, 63 females (mean age 66.77 years) and 53 males (mean age 61.57 years). Recipient age and donor–recipient age mismatch were not significant predictors of graft failure. The mean follow-up time was 527.74 days (range 10–1825 days). Preoperative diagnoses and their relative percentages are shown in Table 1. Thirty percent of the transplants were performed for pseudophakic/aphakic bullous keratopathy, which was the most common preoperative diagnosis in our study, followed by herpetic eye disease, which had a frequency of 19%. Other reasons for transplantation included Fuchs' endothelial dystrophy, infectious scar or perforation, keratoconus, corneal stromal dystrophy, traumatic scar, Aniridia, Peter's

anomaly, sclerocornea, lipid keratopathy, spheroidal degeneration, and silicone keratopathy. This series had a particularly large number of high risk grafts (such as herpes simplex virus, and complicated infections and scars), which needs to be taken into account when generalizing our results to other settings.

There were 44 (37.93%) graft failures, the causes of which are shown in Table 2. Graft rejection was the most common cause of failure (34%), followed by surface diseases (15.9%). Other causes included primary failure, increased intraocular pressure, and infection.

Bivariate analysis was carried out for all primary and secondary predictors collected. A summary of the bivariate results is presented in Table 3. In the bivariate analysis presented in Table 3, any p value less than or equal to 0.10 was included in the multivariate analysis.

Kaplan–Meier survival estimates were produced for 2 age groups from the bivariate analysis. Fig. 1 shows the Kaplan–Meier survival estimate for donor age younger than 65 versus 65 years and older. By day 500, 65% of grafts from donors aged 65 and older had failed compared with 30% from donors younger than 65. Fig. 2 shows the Kaplan–Meier survival estimate for donor age younger than 60 versus older than 70 years. By day 500, 75% of grafts from donors over the age of 70 had failed, while only 25% of grafts had failed in the under-60 age group.

Three models were constructed for our multivariate analysis. Each model looked at the different donor age categories while controlling for other predictors that had a p value less than 0.10 from the bivariate analysis.

The multivariate analysis for donor age showed similar results to the bivariate analysis. Donor age was consistently associated with an increase in the hazard ratio, and the increase became larger as the gap between age categories increased, yet it never reached statistical significance. The continuous age category (Table 4) showed a hazard ratio of 1.004 (p = 0.681). For donor ages younger than 65 versus 65 and older (Table 5), the hazard ratio was 1.17 (p = 0.683). Donor ages younger than 60 versus older than 70 (Table 6) were associated with an increase in the hazard ratio to 2.1 and a p value of 0.089, which is approaching the 0.05 level of statistical significance.

Table 1—Primary preoperative diagnosis for eyes undergoing cornea transplant

Diagnosis	No.	%
PBK/ABK*	34	29.3
Herpetic eye disease	22	19
Fuchs' endothelial dystrophy	17	14.6
Infectious scar/perforation	13	11.2
Keratoconus	5	4.3
Corneal dystrophy	5	4.3
Traumatic scar	4	3.4
Other	16	13.8

*PBK/ABK = pseudophakic/aphakic bullous keratopathy.

Table 2—Causes of graft failures after cornea transplant

Cause of failure	No.	%
Graft rejection	15	34
Surface disease	7	15.9
Primary failure	7	15.9
Increased IOP*	6	13.6
Other	9	20.4

*IOP = intraocular pressure.

Interpretation

Our study demonstrated that the relationship between donor age and graft failure remains unclear. Although the association between donor age and graft failure did not reach statistical significance, we observed consistent increases in the hazard ratio for graft failure as the donor age interval increased. This finding was similar in both the bivariate and multivariate analysis. Had our sample size been larger, it is possible that donor age would have been a significant predictor of graft failure in the widely spaced age category (under 60 vs. over 70 years).

The bivariate analysis revealed some secondary predictors of graft failure to be statistically significant. Sex is generally not considered to be a determinant of graft survival; however, we found that compared with females, males had a higher hazard ratio of failure by 40%. Sit[1] and Maguire[17] both found females were at a lower risk for graft failure. This statistically significant difference was not found in our multivariate analysis.

Table 3—Hazard ratio from bivariate analysis for all predictors of corneal transplant outcome*

Predictors	Hazard Ratio	SE	z	p < [z]	95% CI From	95% CI To
Eye, OS vs OD	0.83	0.26	−0.58	0.56	0.45	1.54
Recipient age, continuous, y	1.00	0.01	−0.53	0.60	0.98	1.01
Sex, F vs M	0.60	0.18	−1.67	0.09	0.33	1.09
Preop logMAR	22.04	23.43	2.91	0.004	2.74	177.09
Preop SVL†, Snellen	2.93	1.07	2.93	0.003	1.43	6.01
Preop *Herpes simplex* or *H. zoster*	2.27	0.71	2.62	0.01	1.23	4.20
Preop glaucoma	1.71	0.64	1.42	0.16	0.81	3.57
Lens status‡	0.97	0.32	−0.09	0.93	0.51	1.84
Graft size, mm	2.14	0.62	2.63	0.01	1.21	3.76
Suture number	0.89	0.05	−2.32	0.02	0.80	0.98
Presence of synechiae	1.32	0.42	0.88	0.38	0.71	2.46
Vitrectomy	1.32	0.42	0.86	0.34	0.70	2.47
Donor age, continuous, y	1.01	0.01	0.58	0.56	0.99	1.02
Donor age, < 65 vs ≥ 65, y	1.25	0.45	0.62	0.54	0.62	2.55
Donor age, < 60 vs > 70, y	2.08	0.89	1.72	0.09	0.90	4.80
Death to cornea harvest, h	1.06	0.05	1.26	0.21	0.97	1.15
Storage time, d	0.93	0.08	−0.81	0.42	0.79	1.10
Endothelial cell count, cells/mm^2	1.00	0.001	−0.46	0.64	1.00	1.00
Postop glaucoma	2.05	0.63	2.34	0.02	1.12	3.73

*SE indicates standard error; CI, confidence interval; OS, left eye; OD, right eye; logMAR measures visual acuity.
†SVL, severe visual loss (< 20/200 vs > 20/200).
‡Lens: phakic or aphakic, PCIOL (posterior chamber intraocular lens) or ACIOL (anterior chamber intraocular lens).

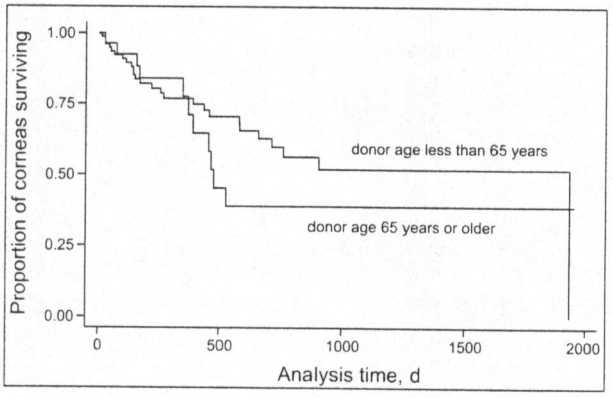

Fig. 1—Kaplan–Meier cornea survival curve as a function of donor age: younger than 65 years versus 65 years and older.

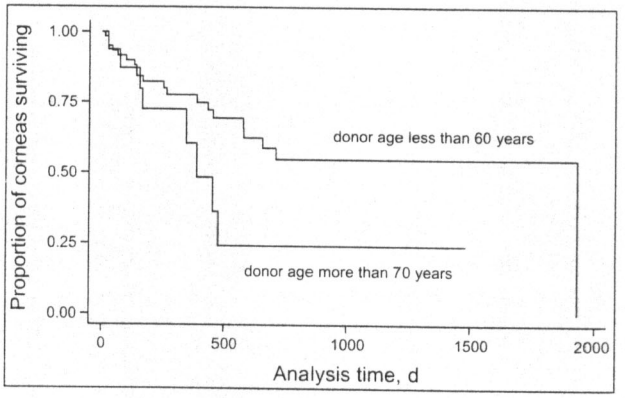

Fig. 2— Kaplan–Meier cornea survival curve as a function of donor age: younger than 60 years versus older than 70 years.

Grafts done in patients with a known history of ocular herpes were at an increased chance of failure in comparison with patients without a known history of ocular herpes disease. This finding is not surprising and has been documented by others.[18] There are several explanations, including corneal vascularization in herpetic corneas, neurotrophic corneas in herpetic eye disease, and recurrence of viral infection and stromal edema posttransplant.

Graft size was associated with an increase in the hazard ratio for failure. In our study, the graft size ranged between 6.5 and 11 mm, while the majority

Table 4—Multivariate Cox hazard model for continuous donor age when controlled to other predictors of corneal graft outcome with $p < 0.10$

Predictors	Hazard ratio	SE	*z*	$p < [z]$	95% CI	
					From	To
Donor age, continuous	1.004	0.01	0.41	0.68	0.98	1.02
Sex, F vs M	0.67	0.23	−1.20	0.23	0.33	1.31
Preop *Herpes*	2.48	0.85	2.67	0.01	1.27	4.84
Graft size, mm	2.52	0.75	3.10	0.002	1.40	4.51
Postop glaucoma	1.61	0.55	1.41	0.16	0.83	3.13

SE indicates standard error; *z* score measures deviation from the mean; CI, confidence interval.

Table 5—Multivariate Cox hazard model for donor age < 65 vs ≥ 65 when controlled to other predictors of corneal graft outcome with $p < 0.10$

Predictors	Hazard ratio	SE	*z*	$p < [z]$	95% CI	
					From	To
Donor age < 65 vs ≥ 65	1.18	0.47	0.41	0.68	0.54	2.56
Sex, F vs M	0.64	0.22	−1.28	0.20	0.32	1.27
Preop *Herpes*	2.37	0.83	2.47	0.01	1.20	4.70
Graft size, mm	2.55	0.76	3.15	0.002	1.43	4.57
Postop glaucoma	1.63	0.55	1.44	0.15	0.84	3.16

SE indicates standard error; *z* score measures deviation from the mean; CI, confidence interval.

Table 6—Multivariate Cox hazard model for donor age < 60 vs > 70 when controlled to other predictors of corneal graft outcome with $p < 0.10$

Predictors	Hazard ratio	SE	*z*	$p < [z]$	95% CI	
					From	To
Donor age < 60 vs > 70	2.11	0.92	1.70	0.09	0.89	4.97
Sex, F vs. M	0.46	0.20	−1.77	0.08	0.20	1.09
Preop *Herpes*	2.93	1.20	2.62	0.01	1.31	6.53
Graft size, mm	3.14	0.96	3.72	0.00	1.72	5.73
Postop glaucoma	1.99	0.79	1.73	0.08	0.91	4.33

SE indicates standard error; *z* score measures deviation from the mean; CI, confidence interval.

of the grafts were between 7 and 8.5 mm. We found that for each 1 mm increase in graft size, the hazard ratio increased approximately 2.5 times ($p < 0.05$) in the bivariate and multivariate analyses. This is consistent with findings of other studies[18–20] and can be explained by the fact that larger grafts extend closer to the limbus, increasing the chance of transplant antigen exposure to recipient blood vessels and eventually increasing the risk of rejection. Furthermore, larger grafts are used in more extensively diseased corneas, which may also affect the prognosis for graft survival.

Postoperative glaucoma was associated with an increased risk for graft failure. Possible explanations for this result include endothelial damage from high intraocular pressure and cornea toxicity from multiple topical antiglaucoma medications.

Any clinical research study may produce erroneous results because of chance, bias, or confounding. With respect to chance, we have mentioned that statistically significant results might have been produced if the sample size were larger. The main bias of cohort studies is loss to follow-up, since it is possible that patients may be differentially followed or lost based on either exposure or outcome variables. We feel this is unlikely for cornea transplantation, however, because all patients were followed with the same examination frequency, and our average follow-up time was similar in all age groups. Finally, to minimize confounding we collected data on all predictor variables and used multivariate methods to minimize their impact.

The question of whether donor age influences cornea transplant success–or not–remains unresolved, yet it is one of the most critical questions in the field of cornea transplantation today. Prospective cohort studies and randomized clinical trials are needed to answer it, and they are needed to clarify the effect of donor age on graft failure between different indications for penetrating keratoplasty. One current study that will help resolve these issues is the Cornea Donor Study funded by the US National Institute of Health, but others will be needed to understand this question completely.

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