Original Investigation

Factors Associated With Corneal Graft Survival in the Cornea Donor Study

Writing Committee for the Cornea Donor Study Research Group

IMPORTANCE The Cornea Donor Study (CDS) showed that donor age is not a factor in survival of most penetrating keratoplasties for endothelial disease. Secondary analyses confirm the importance of surgical indication and presence of glaucoma in outcomes at 10 years.

OBJECTIVE To assess the relationship between donor and recipient factors and corneal graft survival in the CDS.

DESIGN, SETTING, AND PARTICIPANTS Multicenter prospective, double-masked, controlled clinical trial conducted at 80 clinical sites. One hundred five surgeons enrolled 1090 participants undergoing corneal transplant for a moderate-risk condition, principally Fuchs dystrophy or pseudophakic or aphakic corneal edema (PACE). Forty-three eye banks provided corneas.

INTERVENTIONS Corneas from donors younger than 66 years and donors 66 years or older were assigned, masked to donor age. Surgery and postoperative care were performed according to the surgeons' usual routines. Participants were followed up for as long as 12 years.

MAIN OUTCOMES AND MEASURES Graft failure, defined as a regrafting procedure or a cloudy cornea for 3 consecutive months.

RESULTS The 10-year cumulative probability of graft failure was higher in participants with PACE than in those with Fuchs dystrophy (37% vs 20%; hazard ratio [HR], 2.1 [99% CI, 1.4-3.0]; $P < .001$) and in participants with a history of glaucoma before penetrating keratoplasty, particularly with prior glaucoma surgery (58% with prior glaucoma surgery and use of medications to lower intraocular pressure at the time of surgery vs 22% with no history of glaucoma surgery or medication use; HR, 4.1 [99% CI, 2.2-7.5]; $P < .001$). We found trends toward increased graft failure in recipients who were 70 years or older compared with those younger than 60 years (29% vs 19%; HR, 1.2 [99% CI, 0.7-2.1]; $P = .04$) or were African American (HR, 1.5; $P = .11$) or who had a history of smoking (35% vs 24%; HR, 1.6 [99% CI, 0.9-2.8]; $P = .02$). Lower endothelial cell density (ECD) and higher corneal thickness (CT) at 6 months (6% vs 41% for ECD ≥2700 vs <1700 cells/mm^2 [$P < .001$]; 14% vs 36% for CT <500 vs ≥600 µm [$P = .001$]), 1 year (4% vs 39% for ECD ≥2700 vs <1700 cells/mm^2 [$P < .001$]; 18% vs 28% for CT <500 vs ≥600 µm [$P = .04$]), and 5 years (2% vs 29% for ECD ≥1500 vs <500 cells/mm^2 [$P < .001$]; 7% vs 34% for CT <550 vs ≥650 µm [$P < .001$]) were associated with subsequent graft failure.

CONCLUSIONS AND RELEVANCE Most penetrating corneal grafts for Fuchs dystrophy or PACE remain clear at 10 years. The risk for failure is greater for graft recipients with PACE and those with a history of glaucoma. Measurements of ECD and CT during the course of postkeratoplasty follow-up are associated with a risk for failure. However, even with very low ECD and high CT at 5 years, most corneas remain clear at 10 years.

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The Cornea Donor Study (CDS) was designed primarily to evaluate the effect of donor age on graft survival and endothelial cell loss in penetrating keratoplasty for endothelial disease. At 5 years, no difference in graft survival (86%) was found between participants who received corneas from donors aged 12 to 65 years and from donors aged 66 to 75 years.[1] By 10 to 12 years, a small but nonsignificant difference (77% survival for the younger group and 71% for the older group) could be detected.[2] However, the evidence suggested that an age effect at the extremes of the donor age range existed, that is, 96% survival for 80 donors aged 12 to 33 years and 62% survival for 130 donors aged 72 to 75 years.

The effects of recipient, donor, and surgical factors other than donor age on graft survival at 5 years have been reported in prior publications.[3-8] The most prominent finding was that eyes with Fuchs dystrophy had a substantially lower failure rate (7%) than eyes with pseudophakic or aphakic corneal edema (PACE) (27%).[7] Donor endothelial cell density (ECD) had no effect on outcomes, but 6-month postoperative ECD less than 1700 cells/mm^2 and corneal thickness (CT) greater than 600 µm at 1 year were associated with an increased risk for failure at 5 years.[8] Most other factors studied had marginal or no effect on outcomes. The extension of the CDS to 10 to 12 years of follow-up provides opportunities to examine the longer-term effects of donor and recipient factors on graft survival and in particular to assess the relationship of ECD and CT at 5 years to the subsequent course of the grafts.

Methods

Study Protocol

Complete details of the CDS protocol have been reported previously.[1,9,10] The study protocol was approved by the institutional review board at each investigational site (listed at the end of this article). From January 10, 2000, through August 2, 2002, a total of 1090 eligible patients (median age, 72 [interquartile range, 65-76] years) at 80 sites underwent penetrating keratoplasty for Fuchs dystrophy (62%), PACE (34%; 93% for pseudophakic and 7% for aphakic), or another corneal endothelial disorder (4%). Written informed consent was obtained from each participant for the first 5 years of follow-up, and 663 participants who did not undergo regrafting by 5 years renewed consent for follow-up through 2012.

Eligible donor corneas met the standards of the Eye Bank Association of America for human corneal transplantation.[11] Additional donor eligibility criteria included age from 10 to 75 years and an eye bank–measured ECD of 2300 to 3300 cells/mm^2. Median donor age at the time of death was 61 (interquartile range, 52-69) years. Clinical investigators and participants were masked to certain characteristics of the donor tissue, including age and ECD. Donor tissue was assigned without regard to recipient age or other participant characteristics. Preoperative management, penetrating keratoplasty surgical technique, and postoperative care were provided according to each investigator's directive. In the first 6 months of the study, follow-up visit frequency was left to each investigator's routine. Then the minimum follow-up schedule included a visit between months 6 and 12 and then annual visits through 2012. Corneal thickness, measured using an ultrasonic pachymeter per the investigator's usual routine, was optional at postkeratoplasty follow-up visits. Measurements were recorded to the nearest micrometer.

Graft clarity was assessed at each visit. The definition of *graft failure*, based on the definition used in the Collaborative Corneal Transplantation Studies,[12,13] was a second graft or, in its absence, a cloudy cornea with loss of central graft clarity sufficient to compromise vision for a minimum of 3 consecutive months. Details regarding classification of graft failure have been published.[1]

A subset of the CDS participants also consented to participate in the Specular Microscopy Ancillary Study.[4] Preoperative specular microscopic images of the central donor corneal endothelium were provided by participating eye banks. Postoperative specular microscopic images of the central corneal endothelium of the graft were obtained at the 6-month and annual follow-up visits. The preoperative donor images and postoperative recipient images were evaluated for quality and ECD by a central reading center, the Cornea Image Analysis Reading Center (formerly the Specular Microscopy Reading Center) at University Hospitals Eye Institute, Case Western Reserve University, using a previously described variable frame analysis method.[14]

Statistical Analysis

Cumulative probabilities of graft failure (hereinafter referred to as graft failure rates) along with 99% CIs were calculated at 10 years using the Kaplan-Meier method. Proportional hazards regression was used to assess the association of baseline recipient factors with graft failure in univariate and multivariate analyses. Covariates with $P < .10$ were included in a multivariate model to control for potential confounding factors; however, owing to multiple comparisons, only covariates with $P < .01$ were considered statistically significant. The proportional hazards assumption was violated for diagnosis and donor age in the final multivariate baseline recipient factors model. The baseline hazard function was stratified by donor age, but hazard ratios (HRs) were modeled for diagnosis so that the values could be displayed. Results were similar for the other recipient factors when the baseline hazard functions were also stratified by corneal diagnosis (eTable 1 in the Supplement). The association of lens status with graft failure was assessed in separate proportional hazard regressions for patients with Fuchs dystrophy and PACE, with adjustment for participant age and smoking status and stratification of the baseline hazard function by donor age. Additional analyses were performed on the subset of patients who had available ECD and/or CT measurements. Multivariate proportional hazards models were fit conditionally on graft survival at 5.5 years, which was the upper limit for the 5-year visit window. Similar models were run at 6 months and 1 year. No significant deviations from the proportional hazards assumptions were detected for follow-up ECD or CT values.

In all multivariate models, missing data were treated as a separate category for discrete covariates, and a missing value

Table 1. Association of Baseline Recipient Factors and Graft Failure

Recipient Baseline Factor[a]	No. of Patients	10-y Graft Failure (±99% CI), %[b]	Univariate Model		Multivariate Model[c]	
			HR (99% CI)	*P* Value	HR (99% CI)	*P* Value
Age at penetrating keratoplasty, y						
<60	162	19 (±7)	1 [Reference]	.001[d]	1 [Reference]	.04[d]
60-69	284	21 (±6)	1.0 (0.6-1.8)		0.9 (0.5-1.6)	
≥70	644	29 (±5)	1.5 (0.9-2.5)		1.2 (0.7-2.1)	
Sex						
Male	393	24 (±6)	1 [Reference]	.61	NA	NA
Female	697	26 (±5)	1.1 (0.7-1.5)		NA	
Race/ethnicity						
White (non-Hispanic)	1011	24 (±4)	1 [Reference]	.002	NA	NA
African American	50	38 (±17)	2.1 (1.1-4.1)		NA	
Other[e]	29	53 (±28)	2.1 (0.9-5.1)		NA	
Diagnosis						
Fuchs dystrophy	676	20 (±4)	1 [Reference]	<.001	1 [Reference]	<.001
PACE	369	37 (±7)	2.5 (1.8-3.6)		2.1 (1.4-3.0)	
Other[f]	45	23 (±13)	1.7 (0.7-3.9)		1.2 (0.5-2.8)	
Glaucoma history at time of penetrating keratoplasty						
No use of IOP-lowering medications and no prior glaucoma surgery	920	22 (±4)	1 [Reference]	<.001	1 [Reference]	<.001
Use of IOP-lowering medication and no prior glaucoma surgery	99	32 (±12)	1.6 (0.9-2.8)		1.2 (0.7-2.2)	
Prior glaucoma surgery and no use of IOP-lowering medications	26	50 (±24)	2.9 (1.4-6.3)		2.6 (1.2-5.6)	
Prior glaucoma surgery and use of IOP-lowering medications	45	58 (±20)	4.5 (2.5-8.1)		4.1 (2.2-7.5)	
Smoker (at time of surgery)						
No	988	24 (±4)	1 [Reference]	.06	1 [Reference]	.02
Yes	102	35 (±13)	1.5 (0.9-2.5)		1.6 (0.9-2.8)	
History of diabetes mellitus[g]						
No	899	24 (±4)	1 [Reference]	.90	NA	NA
Yes	141	23 (±9)	1.0 (0.6-1.7)		NA	

Abbreviations: HR, hazard ratio; IOP, intraocular pressure; NA, not applicable; PACE, pseudophakic or aphakic corneal edema.

[a] Recipient bed size, vitrectomy in addition to penetrating keratoplasty, and postoperative IOP were all associated with graft failure in univariate analyses but were not associated in multivariate analysis because of confounding with corneal diagnosis or history of glaucoma.

[b] The 10-year Kaplan-Meier estimates are provided for illustration. The proportional hazards models include all follow-up data from surgery to the end of the study.

[c] The multivariate model was generated through stepwise selection of variables with the criterion $P < .10$. The baseline hazard function was stratified by donor age because it violated the proportional hazards assumption. The proportional hazards assumption was also violated for diagnosis. Results were similar when the baseline hazard function was also stratified by diagnosis (eTable 1 in the Supplement).

[d] *P* values are from models with continuous (both linear and quadratic) recipient age.

[e] Includes 8 Asians, 13 Hispanics, and 8 others.

[f] Includes 12 patients with interstitial keratitis, 7 with posterior polymorphous dystrophy, 6 with perforating corneal injury, and 20 with other cause of endothelial failure.

[g] Unknown for 50 patients.

indicator was added for continuous covariates. Similar methods were used to assess the association of donor factors with graft failure. All reported *P* values are 2 sided. Statistical analyses were conducted using commercially available software (SAS, version 9.3; SAS Institute Inc).

Results

Graft failure occurred in 224 of the 1090 participants (21%). In univariate and multivariate analyses, the 10-year graft failure rate was higher in participants with PACE than in those with Fuchs dystrophy (37% vs 20%; $P < .001$) and in participants with a history of glaucoma (glaucoma surgery before penetrating keratoplasty and/or use of medications to lower intraocular pressure at the time of penetrating keratoplasty), particularly when prior glaucoma surgery had been performed (58% in participants with prior glaucoma surgery and using medications to lower intraocular pressure at the time of surgery vs 22% with no history of glaucoma surgery or medication use; $P < .001$) (**Table 1**). We found trends toward increased graft failure in recipients who were older ($P = .04$) or who had a history of smoking ($P = .02$) that did not meet our threshold for statistical significance accounting for multiple comparisons (Table 1). African American race was associated with increased graft failure in univariate analysis ($P = .002$), and this trend was also ob-

Table 2. Association of Lens Status and Graft Failure According to Corneal Diagnosis

Corneal Diagnosis	No. of Patients	10-y Graft Failure (±99% CI), %[a]	Multivariate Model[b]	
			HR (99% CI)	*P* Value
Fuchs dystrophy				
Preoperative phakic; postoperative phakic	153	16 (±7)	1 [Reference]	.62
Preoperative phakic; postoperative pseudophakic[c]	299	18 (±6)	0.9 (0.4-1.8)	
Preoperative pseudophakic or aphakic; postoperative pseudophakic[d]	202	23 (±8)	1.0 (0.5-2.3)	
Postoperative aphakic	22	31 (±19)	1.5 (0.5-4.9)	
PACE				
Postoperative pseudophakic (PC IOL)	218	30 (±9)	1 [Reference]	.02
Postoperative pseudophakic (sutured PCL)	54	30 (±14)	1.1 (0.5-2.5)	
Postoperative pseudophakic (AC IOL)	89	57 (±17)	1.9 (1.1-3.4)	
Postoperative aphakic[e]	8	NR	NR	NR

Abbreviations: AC, anterior chamber; HR, hazard ratio; IOL, intraocular lens; NR, not reported; PACE, pseudophakic or aphakic corneal edema; PC, posterior chamber; PCL, PC lens.

[a] The 10-year Kaplan-Meier estimates are provided for illustration. The proportional hazards models include all follow-up data from surgery to the end of the study.

[b] Models are adjusted for patient age (linear and quadratic terms), smoking status, and baseline hazard function stratified by donor age.

[c] Includes 288 PC, 8 sutured PC, and 3 AC IOLs.

[d] Includes 195 PC, 3 sutured PC, and 4 AC IOLs.

[e] Graft failure rates and HRs are not reported for groups with less than 15 participants.

served in multivariate analysis but did not reach statistical significance (HR, 1.5; $P = .11$).

Further exploration showed that the effects of the recipient's corneal diagnosis and history of glaucoma were primarily limited to the first 5 years after surgery. During the first 5 years, the HR for graft failure for PACE compared with Fuchs dystrophy was 4.3 (99% CI, 2.6-7.1; $P < .001$), whereas, among grafts still functioning at 5 years, the corresponding HR for subsequent failure was 1.1 (99% CI, 0.6-2.1; $P = .65$). Results were similar for individuals with a history of glaucoma: during the first 5 years, the HR for participants with a history of glaucoma surgery and use of medication to lower intraocular pressure at the time of penetrating keratoplasty was 7.2 (99% CI, 3.8-13.5; $P < .001$) compared with patients with no history of glaucoma surgery, and the corresponding HR afterward was 0.5 (99% CI, <0.1 to 7.3; $P = .55$).

Among participants with Fuchs dystrophy, the 10-year postoperative graft failure rate was similar in eyes with postoperative phakia and pseudophakia (16% vs 20%; $P = .34$), with almost all of the pseudophakic eyes having posterior chamber intraocular lenses (IOLs) (96% of 501). Among participants with PACE, graft failure by 10 years was more common when an anterior chamber lens was present postoperatively than with a posterior chamber lens (57% vs 30%; multivariate HR, 1.9 [99% CI, 1.1-3.4]; $P = .02$) (**Table 2**). This HR did not vary meaningfully during the 10 years of follow-up. Eyes with a preoperative anterior chamber lens that was retained postoperatively (n = 81) had a 59% graft failure rate by 10 years, whereas those with an anterior chamber lens exchanged for a posterior chamber lens (n = 28) had a 23% failure rate (multivariate HR, 0.4 [99% CI, 0.1-1.2]; $P = .04$) (eTable 2 in the Supplement). Other than lens status, the effect of the baseline recipient factors on graft failure was similar in participants with Fuchs dystrophy and those with PACE (**Table 3**).

Measurements of ECD and CT at 6 months and 1 and 5 years were strongly associated with an increased probability of subsequent graft failure (**Table 4**). Among participants with a surviving graft at 5 years, the conditional probability of graft failure by 10 years was 29% among 46 participants with a 5-year ECD of less than 500 cells/mm^2 compared with 10% for the 210 participants with a 5-year ECD of 500 to 1499 cells/mm^2 and 2% for the 57 participants with a 5-year ECD of at least 1500 cells/mm^2 ($P < .001$) (Table 4 and the **Figure**, A). With respect to CT, the conditional probability of failure by 10 years was 34% among the 40 participants with a 5-year CT of at least 650 µm compared with 19% among the 97 participants with a 5-year CT of 600 to 649 µm and 8% among the 305 participants with a 5-year CT of less than 600 µm ($P < .001$) (Table 4 and the Figure, B). The correlation between the 5-year ECD and CT measurements was −0.31 (n = 273) (99% CI, −0.41 to −0.20; $P < .001$). Graft failure rates combining the 5-year ECD and CT data are shown in eTable 3 in the Supplement. The addition of preoperative diagnosis in the recipient, glaucoma history, and donor age to the model did not appreciably increase the ability to predict the probability of subsequent graft failure (eTable 4 in the Supplement). As at 5 years, no other donor factors, including eye bank variables and ABO matching, and no operative factors correlated with graft failure at 10 years.

Discussion

Analysis of the CDS data after 10 to 12 years of follow-up largely showed similar associations of baseline recipient factors with graft failure as were seen after 5 years in eyes undergoing penetrating keratoplasty for corneal endothelial disease. Graft failure was again shown to be more likely in participants with PACE than with Fuchs dystrophy and in participants with a history of glaucoma, particularly when prior glaucoma surgery had been performed. In addition, trends suggested higher failure rates in recipients who were 70 years or older or African American or who had a history of smoking. No other donor factors were sig-

Table 3. Association of Baseline Recipient Factors and Graft Failure According to Corneal Diagnosis

Baseline Factor	Preoperative Diagnosis[a]			
	Fuchs Dystrophy		PACE	
	No. of Patients	10-y Graft Failure (±99% CI), %[b]	No. of Patients	10-y Graft Failure (±99% CI), %[b]
Overall	676	20 (±4)	369	37 (±7)
Age at penetrating keratoplasty, y				
<60	126	13 (±6)	29	54 (±23)
60-69	201	19 (±7)	70	25 (±12)
≥70	349	23 (±6)	270	38 (±9)
Sex				
Male	210	16 (±6)	158	36 (±11)
Female	466	21 (±5)	211	37 (±10)
Race/ethnicity				
White (non-Hispanic)	651	19 (±4)	322	35 (±8)
Nonwhite (including Hispanic)	25	43 (±24)	47	45 (±20)
African American	19	32 (±21)	27	42 (±22)
Hispanic	2	NR	9	NR
Other	4	NR	11	NR
Glaucoma history at time of penetrating keratoplasty				
No use of IOP-lowering medications or prior glaucoma surgery	627	19 (±4)	259	31 (±8)
Use of IOP-lowering medications with no prior glaucoma surgery	34	24 (±14)	61	36 (±17)
Prior glaucoma surgery with no use of IOP-lowering medications	8	NR	15	57 (±33)
Prior glaucoma surgery and use of IOP-lowering medications	7	NR	34	68 (±23)
Smoker (at time of surgery)				
No	628	19 (±4)	325	36 (±8)
Yes	48	26 (±14)	44	44 (±20)
History of diabetes mellitus[c]				
No	587	19 (±4)	276	36 (±8)
Yes	67	17 (±10)	69	31 (±16)

Abbreviations: IOP, intraocular pressure; NR, not reported; PACE, pseudophakic or aphakic corneal edema.

[a] Excludes 45 patients with "other" diagnosis.

[b] Graft failure rates were not reported for groups with less than 15 participants.

[c] Excludes 46 additional patients with unknown history of diabetes mellitus.

nificantly associated with graft failure by 10 to 12 years other than the previously reported suggestion of an association between the extremes of donor age and graft outcome.[2] As at 5 years, we found no indication that ABO blood type incompatibility between donor and recipient was important; however, this finding must be viewed in the context that the study eyes were not considered to be at high risk for rejection failure.[6]

During the course of the study, ECD and CT were strongly associated with subsequent graft failure. However, despite these significant associations, neither factor was strongly predictive of graft failure. Even with an ECD of less than 500 cells/mm^2 at 5 years, the probability of graft survival at 10 years was 71%. Likewise, even when the CT was at least 650 µm at 5 years, the probability of graft survival at 10 years was 66%. Combining ECD and CT data with donor age, preoperative diagnosis in the recipient, and glaucoma history did not improve the prediction of success. These data may be useful for clinicians in counseling patients and to provide reassurance that most grafts will remain clear for a number of years, even when the ECD is less than 500 cells/mm^2.

By 10 years, recipient diagnosis remained the most important predictor of outcome, with PACE grafts having failed at almost twice the rate of grafts for Fuchs dystrophy. PACE increased the rate of early failures, but grafts in eyes with PACE that survived the first 5 years had a failure rate from 5 to 12 years similar to that for eyes with Fuchs dystrophy. This finding is consistent with the hypothesis that many eyes developing PACE have a pathologic response to IOL presence that persists after keratoplasty.[7] That is, many eyes with PACE constitute a subset of all pseudophakic eyes: those with poor tolerance of IOLs. Those eyes manifesting this effect of IOLs may drop out of the surviving graft group early, leaving those with PACE not attributable to continued IOL effects after the first 5 years. The lack of effect of lens status in eyes with Fuchs dystrophy and the detrimental effect of anterior chamber vs posterior chamber IOLs in PACE eyes throughout the 10-year follow-up bolster this notion. The postkeratoplasty presence of an anterior chamber IOL was associated with a 1.9-fold increased risk for failure compared with a posterior chamber IOL in PACE eyes. Unlike the overall IOL effect, the detrimental effect of anterior chamber IOLs persisted from 5 to 10 years. This adverse effect of anterior chamber IOLs on graft survival has been noted in the past.[15,16] PACE eyes in which the anterior chamber IOL was replaced with a posterior chamber IOL at keratoplasty had an approximately 60% reduction in the risk for failure, confirming this effect.

Table 4. Association of ECD and CT Measurements During Follow-up With Graft Failure

Follow-up Factor	No. of Patients	Conditional 10-y Graft Failure (±99% CI), %	Multivariate Model[a] HR (99% CI)	*P* Value
Model 1 (Conditional on 6-mo Survival)				
ECD at 6 mo, cells/mm^2 (n = 295)[b]				
≥2700	93	6 (±4)	1 [Reference]	<.001
2200-2699	102	20 (±9)	3.6 (1.0-13.4)	
1700-2199	58	25 (±13)	5.0 (1.3-19.5)	
<1700	42	41 (±18)	10.5 (2.7-40.4)	
CT at 6 mo, µm (n = 641)[b]				
<500	120	14 (±7)	1 [Reference]	.001
500-549	280	19 (±6)	1.5 (0.7-3.1)	
550-599	178	28 (±9)	2.0 (0.9-4.3)	
≥600	63	36 (±15)	2.8 (1.1-6.8)	
Model 2 (Conditional on 1-y Survival)				
ECD at 1 y, cells/mm^2 (n = 368)[c]				
≥2700	83	4 (±3)	1 [Reference]	<.001
2200-2699	105	13 (±7)	2.7 (0.6-12.0)	
1700-2199	92	17 (±9)	3.2 (0.7-14.2)	
<1700	88	39 (±13)	10.0 (2.5-39.3)	
CT at 1 y, µm (n = 633)[c]				
<500	96	18 (±9)	1 [Reference]	.04
500-549	266	18 (±6)	1.0 (0.5-2.4)	
550-599	201	23 (±8)	1.3 (0.6-2.9)	
≥600	70	28 (±12)	2.2 (0.8-5.5)	
Model 3 (Conditional on 5-y Survival)				
ECD at 5 y, cells/mm^2 (n = 313) [d]				
≥1500	57	2 (±2)	1 [Reference]	<.001
1250-1499	25	9 (±7)	6.5 (0.3-127.8)	
1000-1249	30	7 (±6)	4.0 (0.2-94.5)	
750-999	49	7 (±5)	3.5 (0.2-69.7)	
500-749	106	12 (±6)	5.5 (0.4-80.3)	
<500	46	29 (±14)	16.6 (1.1-241.7)	
CT at 5 y, µm (n = 442)[d]				
<550	148	7 (±4)	1 [Reference]	<.001
550-599	157	8 (±4)	1.2 (0.4-3.2)	
600-649	97	19 (±8)	2.0 (0.8-5.3)	
≥650	40	34 (±16)	3.7 (1.3-10.7)	

Abbreviations: CT, corneal thickness; ECD, endothelial cell density; HR, hazard ratio.

[a] Models are conditional on graft survival by the specified time and include patients with CT or ECD values at the specified time. *P* values are calculated from models with continuous ECD and CT values.

[b] At 6 months, 1035 patients had a surviving graft, ECD measurements were missing for 740, and CT measurements were missing for 394.

[c] At 1 year, 985 patients had a surviving graft, ECD measurements were missing for 617, and CT measurements were missing for 352.

[d] At 5 years, 651 patients had a surviving graft, ECD measurements were missing for 338, and CT measurements were missing for 209.

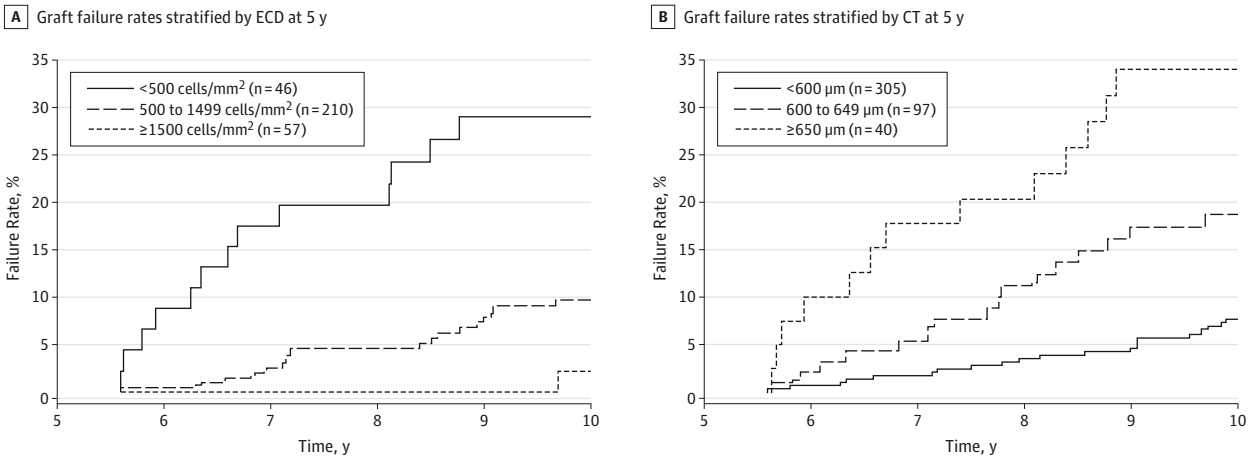
Preoperative glaucoma, particularly prior surgical glaucoma treatment in PACE eyes, also was associated with early failures. Insufficient numbers of participants with glaucoma were available to determine whether this association was true for eyes with Fuchs dystrophy, and data were not collected to evaluate the effect of intraocular pressure control after the first postoperative month. Other studies have associated preoperative and postoperative glaucoma with corneal graft failure in eyes with PACE and Fuchs dystrophy.[17,18] Glaucoma surgery, particularly with tube drainage devices, has been strongly associated with graft failure.[19] These failures are likely related to endothelial cell decline, but the mechanism is unknown.

Diabetes mellitus in recipients did not contribute to graft failure, but we found a trend for a higher failure rate among recipients who smoked compared with those who were nonsmokers. Smoking has been associated with the severity of corneal edema in Fuchs dystrophy.[20] Association of smoking and other risk factors with Fuchs endothelial corneal dystrophy may be mediated through oxidative endothelial damage.[20,21] In addition, trends toward a higher failure rate in recipients older than 70 years and African American recipients were found. An association between nonwhite race and corneal graft failure has been noted previously.[22]

Conclusions

Analysis of the CDS data after 10 to 12 years of follow-up extends our understanding of the association of donor and recipient factors with graft failure in eyes undergoing penetrating keratoplasty for corneal endothelial disease. To our

Figure. Graft Failure Rates Over Time Stratified by 5-Year Endothelial Cell Density (ECD) and Corneal Thickness (CT) Values



Data include participants with a surviving graft at 5 years of follow-up. A, Conditional on graft survival at 5.5 years (upper limit for the 5-year visit window), Kaplan-Meier cumulative probabilities of graft failure (failure rate) are shown for the groups with 5-year ECD values of less than 500, 500 to 1499, and 1500 or more cells/mm^2. B, Conditional on graft survival at 5.5 years, Kaplan-Meier cumulative probabilities of graft failure are shown for the groups with 5-year CT values of less than 600, 600 to 649, and 650 or more µm.

knowledge, the sample size and the duration and completeness of follow-up exceed those of the few other prospective trials of penetrating keratoplasty in the literature. Most grafts after penetrating keratoplasty for Fuchs dystrophy or PACE will remain clear at 10 years. Of the preoperative risk factors studied, the risk for failure is greater for individuals with PACE or with a history of glaucoma. Measurements of ECD and CT during the course of postkeratoplasty follow-up are associated with the risk for failure. However, even with very low ECD and high CT at 5 years, most corneas will remain clear at 10 years. The applicability of the CDS data to endothelial keratoplasty, which has replaced penetrating keratoplasty as the procedure of choice for the corneal endothelial diseases[23] studied in CDS, cannot be predicted. Penetrating keratoplasty may still have advantages in some complex cases requiring IOL exchange or anterior segment reconstruction. The principles examined herein are broadly applicable to endothelial keratoplasty. Trials to further examine donor and eye banking variables for endothelial keratoplasty, such as the ongoing Cornea Preservation Time Study, are warranted.

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