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Corneal Graft Rejection Ten Years after Penetrating Keratoplasty in the Cornea Donor Study

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Abstract

Purpose—To assess the effect of donor and recipient factors on corneal allograft rejection and evaluate whether a rejection event was associated with graft failure.

Methods—1,090 subjects undergoing penetrating keratoplasty for a moderate risk condition (principally Fuchs' dystrophy or pseudophakic corneal edema) were followed for up to 12 years. Associations of baseline recipient and donor factors with the occurrence of a rejection event were assessed in univariate and multivariate proportional hazards models.

Results—Among 651 eyes with a surviving graft at 5 years, the 10-year graft failure (± 99% CI) rates were 12% ± 4% among eyes with no rejection events in the first 5 years, 17% ± 12% in eyes with at least one probable, but no definite rejection event, and 22% ± 20% in eyes with at least one definite rejection event. The only baseline factor significantly associated with a higher risk of

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The following material should appear as supplemental digital content: Tables 1 and 2 Supplemental Digital Content

definite graft rejection was a preoperative history of glaucoma, particularly when prior glaucoma surgery had been performed and glaucoma medications were being used at time of transplant (10-year incidence 35% ± 23% compared with 14% ± 4% in eyes with no history of glaucoma/intraocular pressure treatment, p=0.008).

Conclusion—Those patients who experienced a definite rejection event frequently went on to graft failure raising important questions as to how we might change acute and long-term corneal graft management. Multivariate analysis indicated that the prior use of glaucoma medications and glaucoma filtering surgery was a significant risk factor related to a definite rejection event.

Keywords

corneal graft rejection; penetrating keratoplasty; corneal graft failure

Introduction

The Cornea Donor Study (CDS) examined the relationship between donor age and long-term cornea transplant survival by following for up to 12 years a cohort of 1,090 participants who underwent penetrating keratoplasty (PK), primarily for either Fuchs' dystrophy or pseudophakic or aphakic corneal edema (PACE). At 10 years, there was no significant difference in graft survival between the two main donor age groups (12–65 years and 66–75 years), but there was a suggestion of a donor age effect at the extremes of the age range.[1]

At 5 years, we assessed the effect of donor and recipient factors on corneal allograft rejection. While graft rejection was not associated with donor age, female recipients were more likely to have a rejection event than males and there was a substantially higher graft rejection rate in eyes with PACE compared with eyes with Fuchs' dystrophy.[2] With 10–12 year follow up now completed, we have reassessed factors associated with graft rejection and have evaluated whether a rejection event was associated with subsequent graft failure.

Materials and Methods

Study Protocol

The CDS study protocol, including the Specular Microscopy Ancillary Study protocol has been previously described[3–5] and is briefly summarized here. Institutional review boards at each participating site approved the study protocol, and written consent was obtained from each participant. The 1,090 eligible participants underwent PK at 80 sites for Fuchs' dystrophy (62%), PACE (34%) or another corneal endothelial disorder (4%). Participants' median age at time of transplant was 72 years (interquartile range 65 to 76 years) and donors' median age at time of death was 61 years (interquartile range 52 to 69 years). Surgeons and participants were masked to age and ECD of the donors. Corneal tissue assignment was made without regard to age or any other subject characteristics. Preoperative care, surgical technique, and postoperative care (including prescription of medications), were provided according to each surgeon's customary routine. The number and timing of visits for the first 6 months following PK were left to each investigator's discretion. Thereafter, the minimum follow-up visit schedule included visits at 6 months, 1 year and then annually for 10 to 12 years for those participants who did not require a regraft.

A graft rejection was classified as *definite* when an endothelial rejection line was present in a graft that was previously clear and *probable* when there was inflammation (stromal infiltrate, keratic precipitates, cells in the anterior chamber, or ciliary injection) without an endothelial rejection line in a graft that was previously clear. A graft failure was defined as a regraft or loss of central graft clarity sufficient to compromise vision for a minimum of three consecutive months. Treatment of graft rejection was at investigator discretion.

Statistical Methods

Analyses paralleled those reported after 5 years. Life-tables analysis was used to compute the probability of the first probable or definite rejection event according to the study exam schedule (6 months, 1 year and annually thereafter through 10 years of follow up). Data were censored at the time of a non-rejection graft failure or at the last exam. Associations of baseline recipient and donor factors with the occurrence of a definite rejection event were assessed in univariate and multivariate proportional hazards regression models. Missing covariates in the multivariate models were handled by including missing as a separate category for discrete covariates and adding an indicator for a missing value for continuous covariates. Covariates with $P<0.10$ were included in the final recipient and donor multivariate models generated through stepwise selection to control for any potential confounding; however, only factors with $P<0.01$ were considered statistically significant. The impact of a rejection event on graft failure from all causes was assessed by including graft rejection as a time-dependent variable for definite and probable rejection events in a proportional hazards regression model. Proportional hazards assumptions were checked and no significant deviation was detected for the final models. All reported p-values are two-sided. Statistical analyses were conducted using SAS versions 9.3 software (SAS Institute Inc., Cary, NC).

Results

During follow-up, 133 (12%) of the 1,090 participants had at least one definite rejection episode and an additional 175 (16%) had a probable rejection episode. The 10-year cumulative probability (± 99% CI) for the first definite rejection event was 15% ± 3% and for the first definite or probable rejection event was 34% ± 4% (Figure 1). The 10-year cumulative probability of definite rejection varied by type of corneal disorder: 21% ± 7% for PACE vs. 13% ± 4% for Fuchs' (p=0.002) (Figure 2). However, corneal diagnosis was confounded with glaucoma history (30% for PACE compared with 7% for Fuchs'; Table 1 Supplemental Digital Content). In a multivariate model, corneal diagnosis when combined with lens status was no longer significant, and the only baseline factor significantly associated with a higher risk of definite graft rejection was a preoperative history of glaucoma, particularly when prior glaucoma surgery had been performed and glaucoma medications were being used at the time of transplant (10-year incidence 35% ± 23% compared with 14% ± 4% in eyes with no history of glaucoma/intraocular pressure treatment, p=0.008; Figure 3 and Table 2 Supplemental Digital Content).

The occurrence of a rejection event increased the likelihood of subsequent graft failure. Among 651 eyes with a surviving graft at 5 years, the 10-year graft failure (± 99% CI) rates

were 12% ± 4% among eyes with no rejection events in the first 5 years, 17% ± 12% in eyes with at least one probable, but no definite rejection event, and 22% ± 20% in eyes with at least one definite rejection event (Figure 4). Similarly, in a Cox regression model including all 1,090 eyes over 10 years of follow up, the hazard ratio was 25.0 (99% confidence interval 16.4 to 38.0; $p<0.001$) for the association of a prior definite rejection event as a time dependent factor with subsequent graft failure and 6.1 (99% confidence interval 3.9 to 9.7; $p<0.001$) for a probable rejection event (Figure 4).

One hundred and thirty three patients (12%) experienced one or more definite rejection episodes during the follow-up period. Of these, 41 (31%) responded to treatment and maintained a clear transplant throughout follow up. Further examination of the data related to patients experiencing a definite rejection showed that 22% of PACE patients ultimately cleared as compared with 37% of Fuchs' patients. These calculations are based on a strict definition of a rejection event. If both probable and definite rejection episodes were evaluated, giving us a more relaxed and "inclusive" definition of a rejection, the percentage who experienced one or more definite rejection episodes during the follow-up period increased to 28% with 51% (158) responding to treatment and maintaining a clear corneal transplant. This breaks down to 57% of those with Fuchs responding to treatment as compared to 43% responding with PACE.

Discussion

The CDS sought to determine the impact of donor age on transplant success in a group of 1,090 intermediate risk corneal transplant patients that were followed for up to 12 years. The results and analysis of this have been published.[1] The prospective format of the study also allowed data to be collected regarding specific donor and recipient risk factors and their relationship to corneal transplant rejection and failure. The 5-year results disclosed a statistically significant association between *graft rejection* and corneal diagnosis and female recipient gender.[2] At the same time, a statistically significant association between *graft failure* and corneal diagnosis, a history of glaucoma surgery and, to a lesser extent race was observed.[6] The extended follow up of this population has allowed us to reassess these findings and to look at the relationship between previously identified risk factors as well as the likelihood of a rejection event progressing to graft failure.

The cumulative probability of definite rejection was 10% during the first 5 year period and this increased to 15% by the end of the 10-year follow-up period. Further breakdown according to recipient diagnosis indicated that the cumulative probability of a rejection event among patients with Fuchs' dystrophy was 13% and increased to 21% among those with PACE. The increased probability of a rejection event among the PACE group at 10 years was consistent with the pattern previously noted in the 5 year follow up results.[2] Ing, et. al.[7], reported on the 10 year rejection probability of patients undergoing PK for pseudophakic corneal edema, aphakic corneal edema and Fuchs' as 21%, 28% and 21%, respectively. Their values were more uniform between study groups and noticeably higher in patients with Fuchs' dystrophy as compared with similar measures in the CDS. The cumulative probability, when reassessed in the same patient cohort at 15 years, did not differ between preoperative diagnoses.[8]

In the CDS, lens status in Fuchs' patients did not seem to influence the cumulative probability of a rejection event at 10 years (12 – 13%). The disparity in the rejection rates between Fuchs' patient with IOLs and those with pseudophakic corneal edema suggests that differences in the IOL's used, the status of the vitreous, presence of a peripheral iridectomy, irido-corneal adhesions or the possibility of greater operative or postoperative complications (at the time of primary cataract surgery) might have impacted the intraocular micro-environment permanently. Those in the PACE group did have a higher incidence of glaucoma which was also identified as an independent risk factor for rejection in multivariate analysis. While general information regarding steroid use was documented, the CDS did not collect sufficient data to determine whether the specific steroid used (i.e., prednisolone acetate vs. fluorometholone), the dosing schedule or the cessation of steroids altogether had any impact on the frequency of rejection episodes.

Pre-existing glaucoma is a recognized risk factor for graft failure, but few studies have looked at its relationship to graft rejection.[7, 9–14] Baseline CDS patient data indicated that 30% of those with PACE were on glaucoma medications, had a history of glaucoma surgery (drainage devices/shunts were excluded) or both at the start of the study as compared with 7% of those with Fuchs'. This pattern has been observed in other studies assessing preoperative and postoperative glaucoma in PK patients.[10, 11] While not segregating the data according to diagnosis, multivariate analysis did find a significant increase in definite rejection events in patients who were using glaucoma medications and had prior glaucoma surgery (35% incidence vs. 14% if no glaucoma medications or surgery had been performed) (p=0.008). No association, however, was found between graft rejection and postoperative IOP control. The CDS made no attempt to document how advanced the glaucoma was, however, it is reasonable to assume that patients requiring both glaucoma medications and surgery would have moderate or more advanced disease.

Glaucoma filtering and drainage device surgery have been associated with an increased risk of corneal transplant rejection and failure when performed after PK.[15–18] Presumably this is related to the effect of operative and postoperative trauma and inflammation on the transplant. The influence of glaucoma filtering surgery prior to PK on the incidence of a rejection reaction has not been previously reported. Patients with uncontrolled glaucoma or prior glaucoma filtering surgery where a drainage shunt was placed were excluded from the CDS. Data analysis of baseline recipient and donor factors indicated a relationship with the combination of prior glaucoma surgery and glaucoma medications.

A concern that glaucoma medications may interfere with endothelial function has been raised in the past. Studies that have looked at endothelial status using specular microscopy, pachymetry, and fluorophotometry after extended clinical use of topical bromonidine, beta blockers, dorzolamide and prostaglandin analogs have shown no significant alterations.[15, 18–20] These studies were generally done in normal subjects or those with mild endothelial changes and may not apply to patients with advanced endothelial disease and/or decompensation. Glaucoma medications, either directly or via preservatives such as benzalkonium chloride, have been shown to trigger inflammatory changes within the conjunctiva and adversely alter the tear film and ocular surface. Increased expression of conjunctival and tear pro-inflammatory cytokines (IL-1, Il-6, Il-8, TNF alpha) as well as

HLA-DR and ICAM-1 have been associated with chronic antiglaucoma medication usage.[21–23] Anterior chamber flare has also been reported.[24] It is unknown whether these effects are amplified following glaucoma filtering surgery. Inflammatory changes induced via these mechanisms may explain the CDS findings of an increased incidence of rejection events in patients taking glaucoma medications and having undergone prior glaucoma filtering surgery. The impact of topical steroids (length of time used, potency, and frequency) on this observation could not be assessed.

Price, et.al[25], in a single center 5 year follow up series studying risk factors associated with graft failure in first-time corneal grafts (43.9% with PACE and 24.9% with Fuchs') found an association between glaucoma medication use and graft rejection and failure from immunologic and non-immunologic causes. A lower incidence of glaucoma in their study population (15%) as well as a different definition of glaucoma (glaucoma defined by the use of anti-glaucoma medications only, without regard to prior glaucoma surgery) may account for the lower rejection and graft failure rates (all causes) of 2.1% and 7.5 %, respectively. The impact of steroids on the results of these studies could not be determined.

Donor tissue in the CDS was distributed randomly without regard to donor or recipient age. This allowed us to assess the impact of these factors on the incidence of rejection events, immunologic graft failure and overall graft failure. Neither univariate or multivariate analysis of this medium risk population indicated a relationship. This is consistent with other studies that have looked at rejection episodes[26] and graft failure in single and mixed diagnostic groups[27–32]. Palay et. al.[33], observed an increased incidence of allograft rejections in an age and diagnosis matched adult cohort that received tissue from pediatric donors less than 6 years of age. They attributed this increased risk of rejection to higher histocompatibility antigen expression in very young donors.[34] The CDS did not include donor tissue less than 12 years of age.

ABO compatibility did not impact corneal graft rejection or failure when assessed at the end of the 12 year study period. These findings agreed with the 5 year results.[6, 35] The lack of concordance between the CDS ABO compatibility results and those noted in the Collaborative Corneal Transplant Study in which ABO incompatibility reduced corneal transplant survival[12], may be related to the intermediate risk classification of CDS participants vs. high risk in the Collaborative Corneal Transplant Study.[12] The trend towards higher rejection among ABO compatible pairs in the 10-year CDS multivariate analysis is likely just a spurious result of multiple comparisons that did not meet the criteria for statistical significance. Female gender, which appeared to be a risk factor for a rejection event in the five year analysis, did not remain significant in the 10 year data analysis. The literature supporting a role for gender in graft rejection is contradictory.

The lengthy follow-up period of the CDS allowed us to evaluate the impact of a rejection event on the long-term viability of corneal grafts. Those not experiencing a rejection event during the first 5 years of the study had a cumulative probability of graft failure of 12%. This climbed to 22% for those with definite signs of rejection during the first 5 years. Slightly less than a third of patients experiencing a definitive rejection reaction remained clear at the end of the study period. Further breakdown of this number showed that patients

with PACE fared worse than those with Fuchs' (22% cleared vs. 37%) Once again, we see a poorer outcome for patients with an underlying diagnosis of PACE. We were unable to determine an explanation for this pattern, though the higher incidence of glaucoma in patients with PACE is very likely a factor. To our knowledge, there are no other studies that have looked at the long-term outcome of corneal transplants that have suffered rejection events.

The overall graft failure from all causes was 21% with 34% being related to a definitive graft rejection and 60% being related to non-immunologic causes.[1] The most common non-immunologic cause of graft failure was endothelial decompensation which included patients with probable (but not verifiable and therefore not included in the definite category) rejection reactions. PACE patients had a higher all cause failure rate than Fuchs' patients[1] and a higher failure after a definitive rejection reaction. Patel, et. al.[8], Price, et. al.[25] and Williams, et. al.[18], reported that their all cause graft failure rates were 28% at 15 years, 7.5% at 3 years and 40% and 54% at 10 and 15 years, respectively and that 25%, 27.9% and 34% of their respective graft failures were related to antecedent rejection reactions. Our results compare very favorably with these other studies. Patient populations in studies by Patel[8] and Price[25] were similar to ours, while the study by Williams[18] was a registry study that included regrafts and higher risk patients. These studies did not provide information about the clearance rate/response rate among those patients that experienced a rejection reaction.

In summary, the CDS data documented a 75% 10-year cumulative probability of graft success in this intermediate risk population.[1] The rejection and failure rates were lower than those reported in other studies of shorter duration or mixed patient populations. Those patients who experienced a definite rejection event, however, frequently went on to graft failure (69%) raising important questions as to how we might change acute and long-term management of this group of patients. A distinct pattern was evident in which patients with PACE had a higher rate of rejection events, lower proportion of clearing and corresponding higher failure following a rejection event, and higher all cause failure rate than patients with underlying Fuchs' dystrophy. Multivariate analysis of baseline recipient and donor factors indicated that the prior use of glaucoma medications *and* glaucoma filtering surgery was a significant risk factor related to a definite rejection event. A more comprehensive evaluation of this finding and the role that topical steroids or other anti-inflammatory agents may have in reducing its effect on graft success would be worthwhile. Most studies answer or shed light on some questions and raise new ones – the CDS has definitely done this.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest: Steven P. Dunn, MD, Robin L. Gal, MSPH, Craig Kollman, PhD, Dan Raghinaru, MS, Mariya Dontchev, MPH, Roy W. Beck, MD, PhD, Jonathan H. Lass, MD Mark J. Mannis and Christopher J. Rapuano, MD received institutional grant support as part of the Cornea Donor Study. Christopher L. Blanton, M.D. serves as a consultant, receives lecture fees and grant support from Abbott Medical Optics and serves as a consultant and receives lecture fees Alllergan. Edward J Holland, MD MD is employed by the Cincinnati Eye Bank, serves as a consultant and receives lecture fees from Bausch & Lomb, serves as a consultant and receives

grant support from Abbott Medical Optics, serves as a consultant, receives grant support and lecture fees from Alcon Laboratories, Inc., serves as a consultant and receives grant support from Wavetec Vision Systems, Inc., and serves as a consultant for Senju Pharmaceutical Co., LTD., Wavetec Vision Systems, Inc., and SARCode, TearScience. Jonathan H. Lass, MD is employed by Midwest Eye Banks and Cleveland Eye Bank. Christopher J. Rapuano, MD serves as a consultant and receives lecture fees from Allergan, Bausch and Lomb and Bio-Tissue and serves as a consultant for Merck, Nicox, Tear Lab, and Tear Science.

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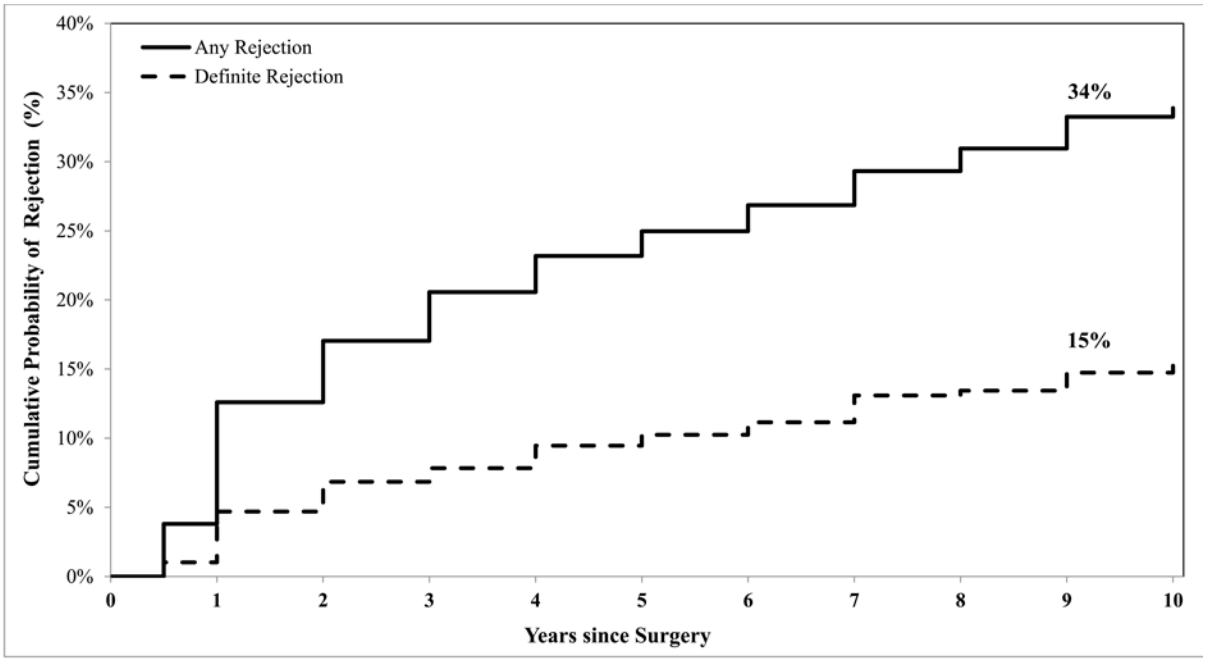


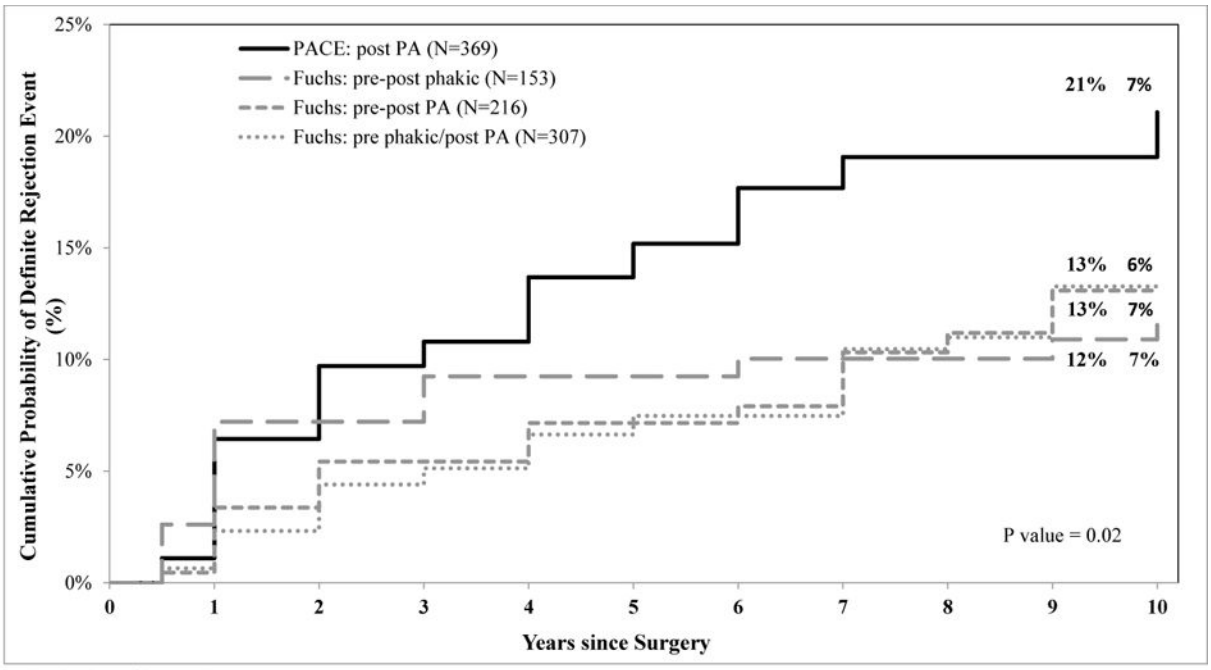
Subjects at risk at beginning of interval:

Any Rejection	1,090	1,026	893	795	724	653	538	485	447	406	365
Definite Rejection	1,090	1,051	960	876	822	749	621	564	524	480	442

Figure 1. Life Table Plot of Cumulative Probability of Any (Probable or Definite) and Definite Rejection Episodes and 10-Year 99% CI (N=1,090)

The table under the figure presents the number of subjects at risk in the beginning of each interval.

CI = confidence interval.



Subjects at risk at beginning of interval:

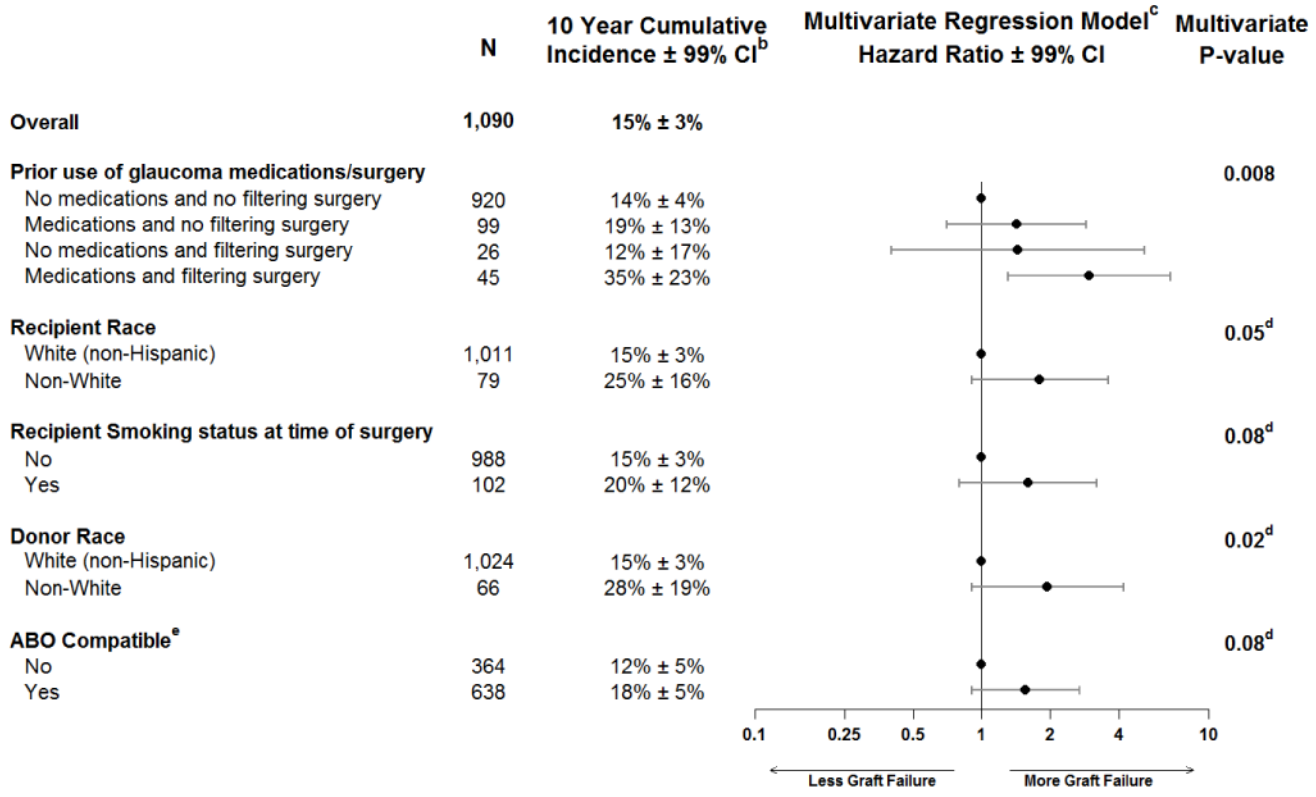
PACE	369	350	299	263	232	194	147	122	112	99	92
Fuchs': pre/post phakic	153	149	140	138	133	130	118	112	110	105	101
Fuchs': pre/post PA	216	210	195	176	170	155	130	118	108	97	88
Fuchs': pre phakic/ post PA	307	300	290	267	257	242	202	189	176	163	146

*Excludes 45 participants with "other" diagnoses

Figure 2. Life Table Plot of Cumulative Probability of Definite Rejection Events by Diagnosis and Lens Status and 10-Year 99% CI (N=1,045*)

Kaplan-Meier cumulative probabilities of graft survival are shown for 4 diagnosis and lens status combinations. With a log-rank test, the p value comparing the four groups was 0.02. The table under the figure presents the number of subjects at risk in the beginning of each interval.

CI = confidence interval.



a - Includes only definite rejection events

b - Kaplan-Meier estimates

c - Multivariate proportional hazards model obtained through backward manual selection, if $p<0.10$

d - P-value does not meet the criteria for statistical significance (<0.01).

e - 88 with missing ABO type

Figure 3. Multivariate Analysis of Baseline Recipient and Donor Factors Predictive of Definite Rejection Event[a]

CI = confidence interval.

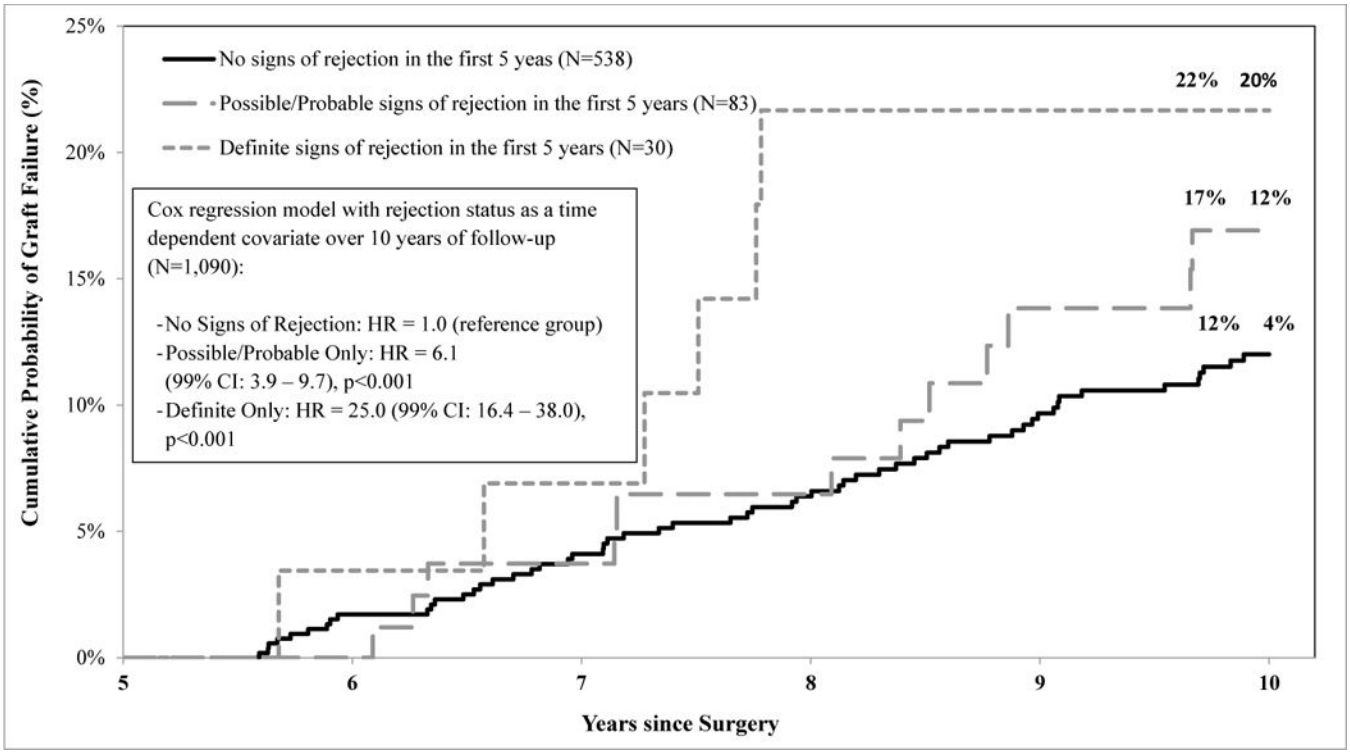


Figure 4. Conditional on 5-Year Graft Survival, Cumulative Probabilities of Graft Failure According to the Strongest Sign of Graft Rejection over the First 5 Years of Follow-up (N=651)

Conditional on graft survival at 5.5 years (upper limit for the 5 year visit window), Kaplan-Meier cumulative probabilities of graft failure and 10-year 99% CI are shown for no rejection, possible/probable rejection, and definite rejection at 5 years.

CI = confidence interval.