Donor Risk Factors for Graft Failure in the Cornea Donor Study

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Purpose: The purpose of this study was to assess the relationship between donor factors and 5-year corneal graft survival in the Cornea Donor Study.

Methods: Donor corneas met criteria established by the Eye Bank Association of America, had an endothelial cell density of 2300 to 3300/mm^2, and were determined to be of good to excellent quality by the eye banks. Donor corneas were assigned using a random approach and surgeons were masked to information about the donor cornea including donor age. Surgery and postoperative care were performed according to the surgeons' usual routines and subjects were followed for 5 years. Donor and donor cornea factors were evaluated for their association with graft failure, which was defined as a regraft or a cloudy cornea that was sufficiently opaque to compromise vision for a minimum of 3 consecutive months.

Results: Graft failure was not significantly associated with the type of tissue retrieval (enucleation versus in situ), processing factors, timing of use of the cornea, or characteristics of the donor or the donor cornea. Adjusting for donor age did not affect the results.

Conclusion: Donor and donor cornea characteristics do not impact graft survival rates for corneas comparable in quality to those used in this study.

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INTRODUCTION

The Cornea Donor Study (CDS) recently published results demonstrating no difference in corneal graft survival at 5 years related to donor age.[1] Although eye banks routinely gather information on both the donor and the quality of the corneal tissue before distributing tissue for transplantation, relatively little information is present in the literature concerning the impact of these factors on graft survival.[2] In the CDS, information on cornea donors, tissue handling, and tissue findings was obtained and assessed to examine any potential impact on graft survival at 5 years. The results of these analyses are presented here.

MATERIALS AND METHODS

Study Protocol

Details of the CDS protocol have been reported previously[1,3,4] and the key aspects are briefly summarized. The study protocol was approved by Institutional Review Boards for each eye bank and at each investigational site.

Eligible subjects were between 40 and 80 years old and had corneal disease associated with endothelial dysfunction and moderate risk of failure (principally Fuchs dystrophy and pseudophakic corneal edema). Written informed consent was obtained from each subject.

Eligible donor corneas met Eye Bank Association of America standards for human corneal transplantation.[5,6] Eligibility criteria for the donor corneas assigned in the study are listed in Table 1. Eye banks obtained information about the cornea donor, including age, gender, race, history of diabetes, and cause of death from medical records, healthcare provider interviews, and family members. Type of tissue recovery, either as whole eye (enucleation) or corneoscleral rim removal (in situ), time from death to placement in preservative medium, body refrigeration time, and death to surgery time were recorded. Specific characteristics of the donor tissue were recorded, including epithelial slit lamp findings, stromal edema, arcus, folds in Descemet's membrane, the presence of "snail tracks" (linear ruptures of endothelial cells), and endothelial morphology by specular microscopy.

TABLE 1. Cornea Donor Study Donor Tissue Eligibility Criteria

Age of donor at time of death: 10–75 years
Death to preservation time: ≤12 hours if body refrigerated or eyes iced and ≤8 hours if not
Death to surgery time: ≤5 days
Donor medical exclusions including cause of death: meets EBAA standards
Donor ocular exclusions: meets EBAA standards for excluding tissue plus no prior intraocular surgery (must be phakic)
Specular microscopy:
• Endothelial cell density 2300 to 3300 cells/mm^2
• Polymorphism/polymegethism—none to no more than mild (slight)
• Guttae—no true guttae
• No evidence of central endothelial cell damage/trauma or dystrophy
Slit lamp examination criteria:
Epithelium
• Defects of 50% or less of epithelium
• Haze—none to no more than moderate
• Exposure—none to no more than moderate
Stroma
• Edema—none to no more than mild
• Arcus—≥8.0-mm clear zone
Descemet's membrane
• Folds—none to no more than few (mild)
Endothelium
• Snail tracks (endothelial stress lines)—none to no more than mild centrally
• Guttae—no true guttae
• No evidence of central endothelial cell damage/trauma or dystrophy.

Clinical investigators and subjects were masked to all characteristics of the donor cornea, including age and endothelial cell density. Preoperative management, surgical technique, and postoperative care (including prescription of medications) were provided according to each investigator's customary routine. The visit schedule during the first 6 postoperative months was at the discretion of the investigator. Thereafter, the minimum follow-up visit schedule included a visit between 6 and 12 months and then annual visits through 5 years. Because of the trial's simple design, data collection at each visit was limited and included an assessment of graft clarity, signs of graft rejection, and intraocular pressure. The definition of graft failure, based on the definition used in the Collaborative Corneal Transplantation Studies,[7,8] was a regraft or, in the absence of regraft, a cloudy cornea in which there was loss of central graft clarity sufficient to compromise vision for a minimum of 3 consecutive months. Further details of the classification scheme for graft failures has been published.[1]

Statistical Methods

The analysis included the 1090 eligible subjects in the CDS. Baseline endothelial cell density was evaluated by the Reading Center for 658 cases. Donor race/ethnicity was excluded from the analysis as a result of the small number of subjects per group (41 blacks, 11 Hispanics, 3 Asians, and 11 other).

Cumulative probabilities of graft failure (subsequently referred to as "graft failure rates") were calculated using the Kaplan-Meier method. Univariate Cox proportional hazards regression models were used to individually assess the association of each donor factor with graft failure. No significant deviations from the proportional hazards assumptions were detected.

All reported P values are 2-sided. Because of multiple comparisons, P values ≥ 0.01 were not considered statistically significant. Statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

RESULTS

The donor characteristics and slit lamp characteristics of the corneas have been reported in detail previously.[3] The distribution of each characteristic is indicated in Table 2.

Among the 135 eyes with graft failures, 102 (76%) had a regraft and 33 (24%) met the cloudy cornea failure criteria defined for the study without a regraft (30 had a cloudy cornea for at least 3 months and 3 had a cloudy cornea for less than 3 months without additional available follow up). Three graft failures were the result of primary donor failure, 8 uncorrectable refractive error, 48 graft rejection, 46 endothelial decompensation, and 30 other causes.

As shown in Table 2, graft failure rates were not significantly impacted by any donor characteristics (gender, history of diabetes, or cause of death); by any factors related to the type of tissue retrieval, processing, timing of use of the cornea (time from death to preservation or time from death to surgery); or by any characteristics of the donor cornea (presence of endothelial polymorphism, endothelial cell damage, Descemet folds, snail tracks, baseline endothelial cell density, epithelial defects, epithelial haze, epithelial exposure, stromal edema, or arcus). Adjusting for donor age did not affect the results (data not shown). When analyses were conducted separately for rejection and nonrejection graft failures, no baseline donor factors were found to be associated with the rate of graft failure based on our prespecified level of significance (data not shown).

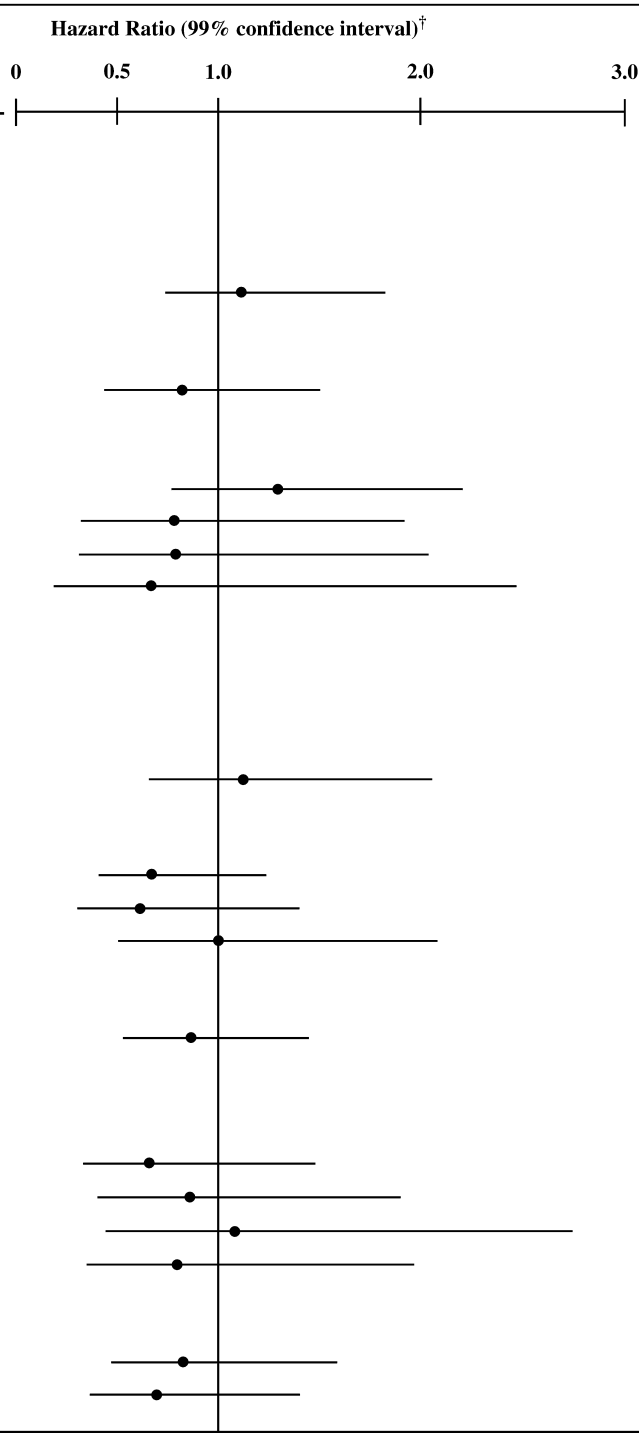
DISCUSSION

Although a number of factors evaluated here have been assessed in other studies, this prospective study is one of the few to address their impact on graft survival. The limitation of this study is that the tissue selection criteria excluded extremes such as prolonged death to preservation time and death to surgery time. Only mild to moderate epithelial, stromal, Descemet, and endothelial variations were accepted. Nonetheless, the information obtained is useful in demonstrating the lack of any adverse impact of the abnormalities found in the ranges studied.

Data on donor cause of death and presence or absence of diabetes mellitus show no impact on 5-year graft outcomes. Earlier studies have shown a similar lack of impact of donor cause of death on 5-year graft survival.[2] Recently, deaths resulting from cancer have been implicated in postoperative endophthalmitis,[9] but there were no cases of endophthalmitis attributable to the donor cornea in the CDS. Additional studies have shown no reason to exclude donors with cancer,[10] but these did not look at graft survival.

TABLE 2. Baseline Donors Factors Predictive of Graft Failure (N = 1090)[1]

Donor Factors	N	5-yr Graft Failure ± 99% CI*
Overall	1090	14% ± 3%
Donor characteristics		
Gender		
Male	716	13% ± 3%
Female	374	15% ± 5%
History of diabetes		
No	891	14% ± 3%
Yes	199	12% ± 6%
Cause of death		
Cardio/Stroke	659	14% ± 4%
Cancer	207	18% ± 7%
Trauma	96	11% ± 9%
Respiratory	78	11% ± 9%
Other†	50	9% ± 12%
Retrieval and timing factors		
Type of Tissue Retrieval		
Enucleation	218	13% ± 6%
In situ	872	14% ± 3%
Time from Death to Preservation		
0–4 hours	206	17% ± 7%
>4–8 hours	577	13% ± 4%
>8 – 10 hours	165	12% ± 7%
>10 hours	142	18% ± 9%
Body refrigerated		
No	255	15% ± 6%
Yes	835	13% ± 3%
Time from death to preservation by refrigeration		
Refrigerated 0 – 4 hours	107	16% ± 10%
Refrigerated >4 –8 hours	433	12% ± 4%
Refrigerated >8 hours	295	15% ± 6%
Not Refrigerated 0 – 4 hours	99	17% ± 10%
Not Refrigerated >4 hours	156	14% ± 8%
Time from death to surgery		
0–<3 days	146	16% ± 8%
3–<4 days	597	14% ± 4%
4–8 days‡	347	12% ± 5%

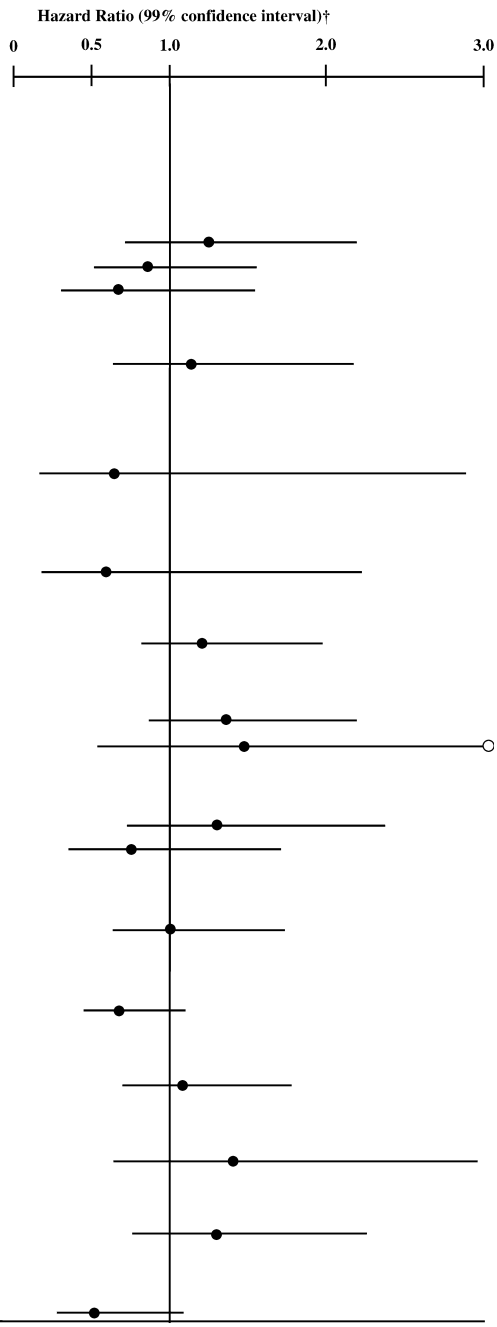


Graft outcome did not differ by method of tissue procurement (enucleation versus in situ retrieval). Rootman and coinvestigators reported no difference in initial donor tissue quality rating by procurement methodology, but they did not look at graft outcomes beyond primary graft failure.[11] A recent study showed no difference in graft clarity at 3 months with either procurement method.[12]

Timing of tissue procurement, refrigeration, and use has been studied in the past and has also been shown, within limited ranges, to have no effect on graft outcome,[2] although prolonged storage times, not studied here, may well have a deleterious effect.[13] Endothelial characteristics likewise had no impact on graft outcomes using the donor criteria of the CDS.[14]

Table 2 continued

Donor Factors	N	5-yr Graft Failure ± 99% CI*
Donor cornea characteristics		
Baseline endothelial cell density§		
2300 – <2500	318	14% ± 5%
2500 – <2700	270	17% ± 6%
2700 – <3000	361	13% ± 5%
≥3000	141	9% ± 7%
Polymorphism/polymegethism		
None	951	13% ± 3%
Mild(slight)/moderate‖	139	16% ± 9%
Endothelial cell damage – diffuse		
None	1054	14% ± 3%
Mild/moderate	36	9% ± 13%
Endothelial cell damage – peripheral		
None	1038	14% ± 3%
Mild	52	8% ± 10%
Epithelium – defects		
Clear and intact	525	12% ± 4%
Defects on <50% of epithelium	565	15% ± 4%
Epithelium – haze		
None	733	12% ± 3%
Mild	315	16% ± 6%
Moderate/severe¶	42	19% ± 17%
Epithelium – exposure		
None	209	12% ± 6%
Mild	661	16% ± 4%
Moderate/severe¶	220	10% ± 5%
Stroma – edema		
None	817	14% ± 3%
Mild/moderate‖	273	14% ± 6%
Arcus present		
None	380	17% ± 5%
Present	710	12% ± 3%
Descemet Folds		
None	376	13% ± 5%
Few (mild)/moderate	714	14% ± 4%
Snail tracks – central		
None	1011	13% ± 3%
Mild/moderate	79	19% ± 12%
Snail Tracks – diffuse		
None	903	13% ± 3%
Mild/moderate	187	17% ± 8%
Snail tracks – peripheral		
None	880	15% ± 3%
Mild/moderate/severe	210	8% ± 5%



a - CI = confidence interval

b - ○ signifies an upper 99% confidence limit > 3.00 (for moderate/severe epithelium – haze group the upper 99% confidence limit = 4.03)

c - 12 anoxia/asphyxiation, 10 renal, 6 hepatic, 4 neurological, 4 drug overdose, 3 gastrointestinal, 3 shock, 2 pancreatitis, 2 seizure, 2 undetermined,1adrenal insufficiency, 1electrocution

d - Includes 17 subjects who received corneas where time from death to transplant longer than five days (15 were six days, 1 was seven days and 1 was eight days)

e - 658 values from the reading center and 432 from the eye bank. Results were similar when excluding the cases without a Reading Center value (data not shown).

f - Only one subject classified as moderate

g - Only one subject classified as severe

Epithelial and stromal changes were generally mild with only one case of severe epithelial exposure and one with moderate stromal edema. Although over half of the donor corneas had epithelial defects, these all involved less than 50% of the epithelium and had no statistically significant effect. Because of the relatively low prevalence of endothelial trauma related to tissue preparation, as manifested by snail tracks in the central cornea and present in only 7% of donor corneas, the impact of this type of trauma cannot be fully assessed.

Although study of more extreme alterations of tissue would be of benefit, this study demonstrates effectively, as have the other reports from the CDS, that all tissue meeting the donor criteria used performs equally well. Continued follow up of this cohort through 10 years is ongoing to assess any potential differences in longer-term survival.

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APPENDIX

A listing of the Cornea Donor Study Investigator Group, including clinical site investigators, eye bank staff, coordinating center staff, specular microscopy reading center staff, and committees, has been previously published online.[1]

The following CDS Publications Committee members independently reviewed and approved this article for submission: John Affeldt, MD, Michael W. Belin, MD, Terry E. Burris, MD, Richard Eifermann, MD, and Jonathan Macy, MD.