Outcome of Primary Adult Optical Penetrating Keratoplasty in a Public Health Service Facility of a Developing Country

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own original work, that I am the owner of the copyright thereof, and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature: Mark D Wagner Date: 2 September 2008

ABSTRACT

Purpose: To evaluate the outcome of primary adult optical penetrating keratoplasty (PKP) at a public health service hospital of a developing country.

Patients and Methods: A retrospective review was performed of the medical records of every patient 12 years of age or older who underwent PKP for keratoconus, corneal edema, stromal scarring, or stromal dystrophy at King Khaled Eye Specialist Hospital in the Kingdom of Saudi Arabia between January 1, 1997, and December 31, 2001, and for whom a minimum of 3 months' follow-up was available.

Results: Of 910 eyes that met the inclusion criteria, there were 464 eyes with keratoconus, 188 eyes with corneal edema, 175 eyes with stromal scarring, and 83 eyes with stromal dystrophy. For the entire group, the probability of graft survival was 96.7% at 1 year, 86.2% at 3 years, and 80.9% at 5 years. Five-year survival probability was best with keratoconus (96.1%), followed by stromal dystrophy (85.9%), stromal scarring (71.1%), and corneal edema (40.3%). The probability of graft survival differed significantly among the surgical indications at all postoperative intervals ($P<0.001$). Factors associated with a significantly increased risk of graft failure on multivariate Cox proportional hazard regression analysis included increasing donor tissue age ($P = 0.005$) and decreasing recipient graft size ($P = 0.02$). Final visual acuity of 20/40 or better was obtained in 409 (44.9%) eyes. Visual acuity of 20/40 or better was obtained in 336 (72.4%) eyes with keratoconus and in 53 (63.9%) eyes with stromal dystrophy but in only 11 (6.3%) eyes with stromal scarring and 9 (4.8%) eyes with corneal edema ($P<0.001$). Overall, improvement in vision occurred in 750 (82.4%) eyes, remained the same in 97 (10.7%) eyes, and worsened in 63 (6.9%) eyes.

Conclusions: The present study has conclusively demonstrated that primary adult optical PKP can be performed at a public health facility in the Kingdom of Saudi Arabia with graft survival and visual results that are comparable to those obtained in well-developed Western facilities. This success is attributed to the presence of a suitable infrastructure that provides modern eye care facilities, donor tissue, and pharmaceuticals to patients who have access to preoperative screening and evaluation, surgical intervention, and postoperative care by well-trained ophthalmologists and ancillary support personnel.

ABSTRAK

Doel: Om die uitkomste van volwasse primêre optiese penetrerende keratoplastiek (PK) by ’n openbare gesondheidsdiens hospitaal in ’n ontwikkelende land te evalueer.

Pasiënte en Metodes: ‘n Retrospektiewe oorsig is gedoen van die mediese rekords van elke pasiënt 12 jaar en ouer wie PK ondergaan het by die King Khaled Oogspesialis Hospitaal in die Koninkryk van Saudi Arabia vir keratokonus, korneale edeem, stromale littekens of stromale distrofie tussen 1 Januarie 1997 en 31 Desember 2001 en vir wie daar ’n minimum van 3 maande se opvolgrekords beskikbaar was.

Resultate: Van die 910 oë wat aan die insluitingskriteria voldoen het, was daar 464 met keratokonus, 188 met korneale edeem, 175 met stromale littekens en 83 met stromale distrofie. Vir die groep as geheel was die transplantaatoorlewing 96.7% teen 1 jaar, 86.2% teen 3 jaar en 80.9% teen 5 jaar. Die vyfjaar oorplantingsoorlewing was die beste vir keratokonus (96.1%), gevolg deur stromale distrofie (85.9%), stromale littekens (71.1%) en korneale edeem (40.3%). Oorplantingsoorlewing het betekenisvol verskil tussen die chirurgiese indikasies tydens alle post-operatiewe intervalle ($P<0.001$). Faktore wat geassosieerd was met ‘n betekenisvolle verhoogde risiko van korneatransplantaat versaking soos per Cox se proporsionele multivariaat risiko regressie analise sluit in skenker ouderdom ($P = 0.005$) en transplantaat grootte ($P = 0.02$). Finale gesigsskerpte van 20/40 of beter is bereik in 409 (44.9%) oë. Gesigsskerptes van 20/40 of beter is bereik in 336 (72.4%) oë met keratokonus en in 53 (63.9%) oë met stromale distrofie maar in slegs 11 (6.3%) oë met stromale littekens en 9 (4.8%) met korneale edeem ($P<0.001$). Oor die algeheel het visie verbeter in 750 (82.4%) oë, dieselfde gebly in 97 (10.7%) en verswak in 63 (6.9%).

Gevolgtrekking: Die huidige studie demonstreer oortuigend dat primêre volwasse optiese PK’s, uitgevoer in ’n publieke gesondheidsfasiliteit in die Koninkryk van Suadi Arabia, vergelykbare transplantaatoorlewing en gesigskerpte uitkomste het as die wat in goed ontwikkelde Westerse fasiliteite uitgevoer word. Hierdie pasiëntsukses word toegeskryf aan die beskikbaarheid van ’n toepaslike infrastruktuur met moderne oogsorg fasiliteite, donor weefsel, geneesmiddels, pre-operatiewe sifting en evaluasie, chirurgiese intervensie en post-operatiewe sorg deur goed opgeleide oftalmoloë en ondersteuningspersoneel.

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I. DEDICATION

This doctoral dissertation is dedicated to all of the physicians who have served as mentors and role models for my career as an academic ophthalmologist.

I would specifically like to acknowledge the following ophthalmologists for their special contributions:

Dr. David Paton, chairman of the Department of Ophthalmology at the Baylor College of Medicine, for guidance through my initial medical student rotations, support through the residency application process, and inspiration to participate in international ophthalmology;

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Dr. Kenneth R. Kenyon, director of the Cornea Service at the Massachusetts Eye and Ear Infirmary, for incomparable fellowship training in cornea and external disease and a quarter-century of fruitful research collaboration.

Drs. Paton, Dohlman, Albert, and Kenyon have provided a lifetime of friendship, encouragement, and support of the professional and personal phases of my career and life. I will always be grateful that I have had the opportunity to have known and worked with these great men.

II. ACKNOWLEDGMENTS

I would like to acknowledge all of the organizations and individuals that contributed to the successful completion of this dissertation.

Corneal transplantation became a reality in the Kingdom of Saudi Arabia as a result of the rapid development of a highly effective ophthalmic infrastructure over the past quarter-century. This achievement would not have been possible without the generous support of the Saudi royal family and the supervision of the Saudi Ministry of Health.

Excellent surgical outcomes are reflective of the herculean efforts of the physicians and staff of King Khaled Eye Specialist Hospital (KKESH) in providing state-of-the-art corneal transplantation services. Special thanks are extended to the ophthalmologists of the Anterior Segment Division, who have performed over 12 000 corneal transplants since the opening of the hospital. Support for this endeavor was provided by the other members of the Department of Ophthalmology, the physicians in the Departments of Anesthesia and Medicine, and the nurses and support personnel of the operating rooms, inpatient floors, emergency room, and outpatient clinics.

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Swailem participated in 4 subprojects associated with this work, which have recently been published or will soon be published in peer-reviewed journals. External consultants, Dr. John Sutphin, Dr. Kenneth Goins, and Dr. Anna Kitzmann, critically reviewed the subproject manuscripts and the final version of this dissertation. Dr. Bridget Zimmerman provided invaluable contributions with biostatistical analysis.

Finally, I would like to acknowledge the contribution of this project's promoter, Professor David Meyer, for his efforts in suggesting the performance of this project and in guiding it through all stages of development and completion.

III. INTRODUCTION

In the second half of the 20th century, the Kingdom of Saudi Arabia (KSA; also referred to simply as "the Kingdom") utilized the wealth generated by its vast oil reserves to develop and modernize every endeavor in the country, including health-care services.[1]

The Ministry of Health (MOH), which administers more than 200 hospitals and 30 000 inpatient beds, is the major provider of health-care services in KSA.[2] In addition to the services offered by the MOH, other government agencies, such as the Ministry of Defense, the National Guard, the Ministry of Higher Education, and the Ministry of the Interior, operate hospital facilities that provide general medical care, including ophthalmic services, to their employees and dependents. In addition, private medical services, which have undergone remarkable growth and development over the last decade, have eased the burden of providing health care to the rapidly growing Saudi population, which is approaching 20 million citizens.

The MOH utilizes a pyramidal system of primary, secondary, and tertiary care centers, similar to systems used in Western countries with public health services.[3] This system has the advantages of logical allocation of material and personnel resources and stratification of care based upon complexity. Disadvantages include inevitable delays in referral and transfer of patients for higher levels of care, long travel distances for tertiary care, and surgical waiting lists, especially for patients with less severe conditions.

The objective of this dissertation has been to examine the public health service infrastructure that has been developed for the provision of corneal transplantation (keratoplasty) services in KSA. To fulfill this objective, a review was conducted of the outcomes of primary adult optical penetrating keratoplasty (PKP) performed at King Khaled Eye Specialist Hospital (KKESH) between 1997 and 2001. These dates were selected because they provide an opportunity to assess the system after sufficient time

had elapsed for maturation of the infrastructure and for evaluation of surgical results following a sufficient interval of postoperative follow-up.

Corneal Transplantation in Developing Countries

Much progress has been made in recent years in formulating strategies to combat blindness that is curable and preventable in the developing world.[4-11] However, as much as 15% of blindness in developing countries is caused by bilateral corneal opacities, which are usually related to infectious diseases and nutritional disorders.[5-7, 12-17]

Because of high costs and logistical difficulties associated with the implementation of large-scale, successful keratoplasty programs in developing countries that are afflicted with a large burden of corneal blindness, public health initiatives are usually directed toward the prevention and treatment of disorders that lead to the loss of corneal clarity.[4,9,11,18] These include eradication of trachoma in communities in which it is endemic and surgical correction of eyelid abnormalities associated with subsequent development of corneal scarring,[12,13,17,19-21] elimination of vectors associated with onchocerciasis and antibiotic treatment of infected individuals,[17] provision of measles vaccination,[6,7] and establishment of nutritional programs that provide vitamin A through supplemental dosing or improved diet.[6,7,16,22]

The key to solving the problem of blindness from corneal scarring in developing countries lies in prevention rather than cure.[4] However, once the damage has occurred, keratoplasty can play a role in relieving visual disability in affected individuals.[5,9] Although it is a relatively simple matter to perform corneal transplants in well-developed Western countries because of extensive health-care infrastructure, well-equipped operating theaters with well-trained support staff, and easy access for adequately motivated patients for follow-up care, it is often not possible to duplicate these services in many developing countries.[4,11]

The institution of an appropriate and potentially successful keratoplasty program requires a high level of development and sophistication of the following key ingredients[4]:

1. *Facilities*. Modern, sterile surgical theaters with operating microscopes and appropriate microsurgical instruments are essential for performing keratoplasty. Ideally, services are best concentrated in tertiary care centers because high-volume keratoplasties performed in a few centers tend to produce better results than those performed with less frequency at small sites.[23]

2. *Personnel*. Well-trained ophthalmologists with experience in keratoplasty are necessary to optimize results. Previous studies have demonstrated that cases performed by subspecialists are more likely to fare better than those done by general ophthalmologists.[24]

3. *Donor tissue*. Keratoplasty is not possible without access to a reliable source of fresh or preserved donor tissue.[25-28] Most developing countries lack the financial resources to acquire tissue from international sources or to establish their own eye banks.[11,29-31] When present, local eye banks often face considerable difficulty in acquiring local tissue because of the lack of political influence to establish and/or change human donor laws, and the existence of religious beliefs or superstitions condemning the donation of human tissue for organ transplantation.[4,11,32] However, these barriers are not insurmountable, as demonstrated by the successful creation of an eye bank in Sri Lanka, which has supplied thousands of corneas to Middle Eastern and Asian countries.[33]

4. *Pharmaceuticals*. Medications essential for the pre-, intra-, peri-, and postoperative management of keratoplasty must be available and affordable for patients. Prolonged topical treatment with corticosteroids is mandatory for prevention and treatment of immune-mediated graft rejections and for development and progression of corneal

neovascularization.[34-44] Antibiotics are required for prevention of infections and treatment of suture- and ocular surface-related microbial keratitis and endophthalmitis.[45-53] Systemic and topical glaucoma medications must be available for management of the common occurrence of elevated intraocular pressure (IOP).[54-58] Topical and systemic antiviral therapy is mandatory for keratoplasty related to ocular herpetic disease.[59-61] Topical and systemic cyclosporine may be helpful in preventing endothelial rejection episodes, especially in high-risk keratoplasty.[62,63]

5. *Patient access*. Patients must have access to entry into the eye care system for initial evaluation, to affordable surgical interventions, and to the routine and emergent postoperative care that is essential for maximizing the opportunity for graft survival and a good visual outcome.[4,11,64,65] Many patients in developing countries live in remote areas relative to the treatment center and find it either too time-consuming or costly to comply with the rigid postoperative surveillance and care requirements.[4,11]

6. *Patient compliance.* Physical access to postoperative care and availability of appropriate pharmaceuticals alone are insufficient to ensure successful keratoplasty outcomes if patients are not compliant with the visit schedule or proper use of the medications. Two common reasons for patient noncompliance are ignorance and a lifestyle that places a higher priority on other activities. For example, it may be perceived that it is more important for keratoplasty recipients to work in the fields to support their families than to seek medical attention when symptoms of graft rejection are noted. Patients may not understand, remember, or recognize the significance of graft rejection signs and seek care even if unencumbered with alternative responsibilities.

Corneal Transplantation in the Kingdom of Saudi Arabia

In the last 25 years, keratoplasty has evolved from a near nonexistent procedure to one that is performed annually more than a 1000 times Kingdom-wide.[1] The creation of a

national tertiary care eye center was the germinal event that established the infrastructure necessary to realize this remarkable health-care development.[1-3,66]

King Khaled Eye Specialist Hospital

The beginning of modern ophthalmology in KSA, and the first steps toward establishing the appropriate national infrastructure for a successful keratoplasty program, was marked by the opening of King Khaled Eye Specialist Hospital (KKESH).[1] In 1975, Dr. Hal Mackenzie Freeman, a retinal surgeon from the Massachusetts Eye and Ear Infirmary, operated on a member of the Saudi royal family in Boston, Massachusetts. During his visits to KSA to provide follow-up care, he became acquainted with King Khaled bin Abdulaziz Al-Saud and suggested the construction of a world-class eye facility in KSA. In 1978, King Khaled issued a royal order to build a 50-bed eye hospital in Riyadh. Later, the scope of the plan was expanded by Minister of Health Dr. Hussein A. Gezairey for a 263-bed facility. The hospital was opened for patient care on December 21, 1982, under the direction of H.E. Dr. Samer Islam (supervisor general) and Dr. David Paton (medical director).

Consistent with findings from a 1984 nationwide survey, which found that over 70% of blindness in KSA was caused by cataract and corneal disease,[21] a substantial portion of the initial material and personnel resources of KKESH was allocated toward the development of a large Anterior Segment Division to evaluate and provide surgical intervention for these conditions. From an initial staff of 12 full-time, subspecialty fellowship-trained ophthalmologists, the Anterior Segment Division has gradually expanded to its current roster of 20 budgeted positions.

Initially, the surgical staff positions of the Anterior Segment Division were filled almost exclusively with expatriate physicians, mostly from North America, with the intention of gradually moving highly qualified Saudi ophthalmologists into these positions as they became available. Although some Saudis had benefited from limited training in the

United Kingdom, Germany, Canada, and neighboring Middle Eastern countries, the impracticality of relying upon these foreign programs as the primary means of producing the first generation of Saudi ophthalmologists soon became apparent.[67]

Using the American residency training model, the first ophthalmic residency training program was initiated on October 1, 1984, as a joint project of KKESH (under the directorship of Dr. David Paton and Dr. Ihsan Badr) and the newly established Department of Ophthalmology at King Saud University Medical College (under the direction of Dr. Khaled Tabbara).[67] On September 30, 1989, 13 ophthalmologists graduated from this 4-year program. Smaller residency training programs were also established in affiliation with university ophthalmology programs in Jeddah and the Eastern Province. Subsequently, the Saudi Council of Health Specialties established the Scientific Board of Ophthalmology (under the direction of Dr. Ali Al-Rajhi) to accredit and standardize the curriculum of residency training in KSA and to provide certification examinations for their graduates. In November 1998, graduates of the Greater Riyadh Residency Program and those of the regional residency programs in Jeddah and the Eastern Province sat for the first written and oral examinations of the Scientific Board of Ophthalmology, and successful candidates were awarded the Saudi Specialty Certificate in Ophthalmology (SSCO). To date, more than 250 Saudi ophthalmologists have successfully completed training in these programs, and received board certification.

On October 1, 1994, KKESH initiated the first formal ophthalmic subspecialty fellowship training program in KSA. The goals were to provide clinical training in each major area of ophthalmology and to produce subspecialty graduates, some of whom would gradually replace expatriate subspecialists at KKESH ("Saudization") and others who would facilitate the introduction and provision of tertiary care services to the regional medical centers ("decentralization"). More than 125 ophthalmologists have graduated from these subspecialty programs. Today, 34 Saudi graduates of the Greater Riyadh Residency Program and the KKESH subspecialty fellowship program are full-

time KKESH faculty members, including 18 subspecialists in the Anterior Segment Division.

The KKESH Eye Bank

Corneal transplantation was first performed at KKESH on June 1, 1983, utilizing tissue obtained from the Houston Eye Bank.[68] As a means of providing tissue for large numbers of patients with corneal blindness requiring treatment, the KKESH Eye Bank was established in 1984 to serve the needs of the hospital's patients and ophthalmologists. In 1986, it became an international member of the Eye Bank Association of America (EBAA), thereby establishing itself as the center for Kingdom-wide procurement and distribution of corneal tissue.

Initially, all donor tissue was procured from eye banks in the United States and from one eye bank in the Far East. Because of a higher incidence of postoperative endophthalmitis associated with the use of tissue from the Far Eastern eye bank,[69,70] a decision was made in 1991 to obtain international tissue exclusively from EBAA-certified eye banks in the United States.

The high cost of foreign tissue procurement, combined with the extraordinary demand for keratoplasty, has made local tissue procurement a high priority. Support of local tissue and organ donations in the Kingdom was made possible by a fatwa issued by majority decision of the nation's highest religious authority, the Senior Ulama Commission, which granted "the permission to remove an organ or a part hereof from a dead person for the benefit of a Muslim, should the need arise and should the removal cause no dissatisfaction and the transplant likely to be successful."[71] Since then, the Saudi Center for Organ Transplantation (formerly known as the National Kidney Foundation) has established highly successful programs for organ donation, especially for renal transplantation.[71] The KKESH Eye Bank conducts an annual training course in corneal retrieval techniques for allied health-care personnel from regional health centers.

In addition, public awareness programs are being organized to increase public acceptance of the value of corneal donation. Enthusiasm for eye donation has unfortunately lagged behind that of internal organs. To date, local donors account for less than 5% of transplanted corneas. However, optimism exists that local donation will eventually replace the need for acquiring foreign tissue and will provide sufficient volume to meet the demands of the Kingdom.

The KKESH Eye Bank has played an important role in ensuring that a sufficient supply of donor material is available to meet the keratoplasty demands of KSA. In the 1980s, approximately 400 corneal transplants were performed annually in KSA, with more than 95% of these carried out at KKESH. Between 1983 and 2002, 11 609 corneal transplants were performed in KSA, of which 8318 (71.7%) were done at KKESH. Today, more than 1000 transplants are performed annually in KSA, of which approximately 700 (70%) are conducted at KKESH.

Keratoplasty Services

All Saudi citizens with ophthalmic disorders requiring tertiary care, including corneal disorders associated with visual impairment, are eligible for government-sponsored care at KKESH.[66] Patients who qualify for care by virtue of meeting the tertiary guidelines of the hospital have access to an initial evaluation of their ophthalmic disorder, admission for indicated medical or surgical intervention, government-sponsored transportation to and from Riyadh (if not from the central region) for all scheduled postoperative visits, and provision of all necessary pharmaceuticals at no cost.

To minimize costs associated with travel to Riyadh, most patients who live outside the central region are initially evaluated by ophthalmologists in secondary (regional) health-care centers. Patients with corneal disorders that are potentially amenable to surgical intervention are reviewed by a local General Medical Committee (GMC), which sends a formal ophthalmic report to the KKESH Medical Coordination and Eligibility

Department (MCED). The report is reviewed by the chief of the MCED, in conjunction with the chief of the Anterior Segment Division. Initial patient approval is based on a visual "need to see" rather than a favorable prognosis. The patient is then placed on the new patient waitlist, and within a reasonable period of time (1 to 3 months), an appointment is given with a faculty member of the Anterior Segment Division.

Patients living within the greater Riyadh area may gain admission to KKESH through the Riyadh GMC or through similar eligibility evaluations that are conducted daily at the KKESH Screening Clinic. This facility is adjacent to the main hospital and provides daily screenings of patients who present for determination of whether or not they have a tertiary care disorder that meets the hospital's eligibility guidelines. If the full-time ophthalmologist in the Screening Clinic determines that the patient has visual disability caused by a corneal disorder that is amenable to keratoplasty, a new patient file is opened and the patient is placed on the patient waitlist.

The third mechanism for entry into the system is through the Emergency Room (ER). Patients with acute corneal disorders may be given follow-up appointments in the Anterior Segment Division after completion of management in the ER or in the inpatient units. Examples of acute cases arising from the ER that may ultimately require optical, rather than therapeutic, PKP include post-infectious scarring after resolution of herpetic, bacterial, or fungal keratitis, and post-hydrops keratoconus.

At the time of the initial evaluation in the Anterior Segment Division, the treating ophthalmologist determines whether or not the patient will benefit from keratoplasty. A determination of potential surgical benefit requires no additional internal or external approvals with respect to authorization of the patient for all recommended services and care at no cost, including inpatient admission for the procedure, all required medications, and follow-up visits.

If surgery is indicated, the patient is sent to the Pre-Hospitalization Unit of the Department of Medicine for a complete history, physical examination, chest X-ray, and laboratory screening to identify any medical contraindications to local or general anesthesia and to provide any interventions that are necessary to optimize the general medical well-being of the patient. For many patients, this is their first thorough medical examination, and many previously undetected serious medical problems, such as hypertension and diabetes mellitus, are identified during these preoperative screenings.

After obtaining medical clearance for scheduling surgery, the patient then proceeds to the KKESH Eye Bank to be placed on the waitlist for the indicated procedure. Initially, almost all corneal transplants were scheduled as PKPs, although an increasing number of lamellar keratoplasties (LKPs) are being performed today. Appropriate preoperative counseling is provided by one of the eye bank technicians about the admission process, the surgical procedure, and the follow-up regimen. Today, approximately 250 patients are on the waitlist at any given time, with an approximate waiting time of 3 months.

In recognition of the paramount importance of patient compliance in successful keratoplasty, extensive counseling of the procedure and postoperative care and medication regimens are provided by the KKESH Eye Bank. In addition, patients meet with instructors from the Department of Education, where they are provided with additional verbal and Arabic written information about the procedure. Patients may utilize the Social Services Department to obtain assistance with planning travel and accommodation logistics for themselves and accompanying family members for their surgery and subsequent visits to the hospital. The Departments of Education and Social Services remain available during the entire clinical course for ongoing intervention, if necessary.

Keratoplasty procedures have always been performed as inpatient procedures at KKESH. Inasmuch as costs associated with inpatient surgery have not been a rate-limiting issue, inpatient surgery has provided logistical ease for patients (especially those

from outside the central region). Since the initiation of ambulatory surgery at KKESH in 1994, many procedures (especially cataract and oculoplastic procedures) are routinely done as outpatient procedures with excellent results. Nonetheless, keratoplasty strictly remains an inpatient procedure.

Patients who are next on the waitlist are called by the KKESH Eye Bank and are brought to the hospital for surgery when tissue becomes available. The Pre-Hospitalization Department repeats the medical evaluation and writes admission orders necessary for treatment of existing medical conditions, as well as interim interventions to optimize the safety of local or general anesthesia. The attending ophthalmologist reexamines patients to verify that their medical status has not changed and approves the tissue that has been offered by the KKESH Eye Bank. The surgical procedure is performed on the day after admission. Patients remain in the hospital until reepithelialization of the graft is complete. Most patients are discharged within 5 to 7 days, although approximately 10% of patients require an additional week of hospitalization. They are discharged with a sufficient supply of medications to last until the first postoperative visit, which generally takes place 1 to 2 weeks after discharge.

Patients who live in the central region generally drive to KKESH for their postoperative appointments. Because of local religious and cultural restrictions, female patients may not drive themselves to their appointments and must be accompanied by a close male relative. Patients who live outside the central region have to fly to Riyadh for their postoperative appointments. Airline transportation is provided to and from all scheduled appointments by the national airline carrier, Saudi Arabian Airlines, at no cost to the patient and a traveling companion. The inclusion of a traveling companion is particularly applicable for female patients who must travel with a close male relative; however, most elderly male patients also choose to be accompanied to their postoperative visits by a younger member of their immediate or extended family. At the time of each postoperative visit, medication prescriptions are written for patients by the attending

ophthalmologists, and a sufficient supply is dispensed by the pharmacy for the visit interval.

To ensure compliance with the management of postoperative complications, all patients who develop endothelial rejection episodes, bacterial keratitis, endophthalmitis, retinal detachments, or late-onset persistent epithelial defects are admitted for inpatient management. Unless surgical intervention is required, glaucoma worsening is managed on an outpatient basis.

Changing Indications for Keratoplasty

The maturation of the infrastructure of keratoplasty services in KSA occurred in parallel with socioeconomic development and population growth, resulting in remarkable changes in the surgical indications for which keratoplasty is performed.[72] The greatest impact of the initial backlog of cases, which was dominated by patients with post-trachomatous scarring, was reflected in the large number of procedures (>50% of total cases) performed for stromal scarring between 1983 and 1987, whereas the greatest impact of changing socioeconomic conditions, which have virtually eliminated active trachoma, was manifest in the large reduction in the number of procedures (<20% of total cases) performed for the same condition between 1997 and 2002.[72]

According to the findings of a 1984 survey, corneal disease accounted for 20% of cases of blindness in KSA, with the majority of cases caused by chronic trachoma.[21] For many years, active trachoma was a serious ophthalmic problem in the Kingdom.[12-14,20,21] In 1984, 6.2% of the Saudi population had evidence of active trachoma and 22.2% of Saudis had evidence of active or inactive trachoma.[20] Up to 1.5% of Saudis had trichiasis or entropion caused by previous infection.[20] Dramatic improvements in hygienic standards have virtually eliminated active trachoma from the Kingdom.[12,13] At the same time, there has been a gradual attrition of the large population of elderly Saudis with trachomatous scarring as a result of inevitable aging and death. By 1994, only 2.6% of

the Saudi population had active trachoma.[20] Within a decade, the percentage of those with evidence of active or inactive disease had fallen from 22.2% to 10.7% of the population.[20] Entropion or trichiasis from healed trachoma affected only 0.2% of the population.[20] The contribution of trachoma as a cause of corneal blindness and visual impairment also declined with the shrinking burden of eyes with entropion and trichiasis, and corneal scarring that resulted in many of these cases.[12-14,19,73] The prevalence of vision impairment attributed to trachoma declined significantly from 2.1% in 1984 to 0.3% in 1990 in the Eastern Province.[14,73] According to a 1995 survey, visual impairment from trachoma was 0.95% in the southwestern region of KSA.[13] In the absence of new cases, continued aging and death of elderly individuals will eventually eliminate trachoma-related visual disability from the population. In the interim, the need to provide visual rehabilitation for patients with trachomatous corneal scarring remains a public health issue.

The greatest impact of the rapid population growth in the last 20 years has been on the increase in the number of corneal transplants performed for keratoconus.[72] Between 1983 and 2002, the Saudi population doubled to approximately 17 500 000 people, of whom approximately 43% are under the age of 15 years and approximately 18% are between the ages of 15 and 24 years (www.saudi-online.com; www.esa.un.org). During the same period of time, the annual percentage of corneal transplants performed for keratoconus at KKESH increased from approximately less than 10% to greater than 40% per year, making it the leading indication for keratoplasty today in KSA.[72] Within the region, keratoconus is also the largest contributing diagnosis for keratoplasty in Israel[74-76] and Iran.[77] In Western countries, keratoconus is the leading indication for keratoplasty only in New Zealand.[78]

The prevalence of keratoconus as the leading indication for keratoplasty in KSA contrasts sharply with the experience in the United States and Canada, where keratoconus accounts for only about 15% of corneal transplants.[79-83] Although there is no firm epidemiological data to suggest that the prevalence of keratoconus is actually

higher in KSA than in the United States, the recent population explosion has undoubtedly increased the number of affected individuals in KSA. When present, keratoconus seems to progress more rapidly[84,85] and is more frequently associated with other disorders, such as vernal keratoconjunctivitis (VKC), in KSA than in the United States.[86] The median age at the time of surgery for keratoconus is only 21.5 years at KKESH,[86] compared with a median age of 40.6 years for a large series of keratoconus patients who underwent surgery at the Wills Eye Hospital in the United States.[83] The earlier age of surgical intervention that has been documented in eyes with concomitant keratoconus and VKC lends anecdotal support to the hypothesis that ocular rubbing in response to chronic itching may contribute to the progression of the disease in these patients.[86]

Unlike in Western countries, where corneal edema in aphakic and pseudophakic eyes has constituted the leading indication for keratoplasty since the early 1980s,[80-83,87-98] it has been a less prevalent indication for PKP than corneal scarring and keratoconus in KSA.[72] In developed countries, the implantation of large numbers of iris-plane and closed-loop anterior chamber intraocular lenses (AC IOLs) in the 1970s resulted in a subsequent "epidemic" of aphakic and pseudophakic corneal edema,[87] which has continued to be the leading indication for keratoplasty from the early 1980s to the present day. Prior to 1983, cataract surgery was not frequently performed in KSA, thereby resulting in far fewer iris-plane and closed-loop AC IOLs being implanted than in the United States. Nonetheless, variability in the training and skills of ophthalmic surgeons in the Kingdom at that time, as well as the use of unsatisfactory intraocular lens design, created a small backlog of eyes with postoperative corneal edema. Still, pseudophakic corneal edema never became the leading indication for keratoplasty at KKESH. It should be pointed out that keratoplasty for phakic corneal edema is much less common in KSA, primarily because of a much lower prevalence of Fuchs' endothelial dystrophy. Since the opening of KKESH, fewer corneal transplants have been performed for Fuchs' endothelial dystrophy than for phakic corneal edema caused by congenital hereditary endothelial dystrophy,[72] a condition that is much more common in KSA than in Western countries.[99]

From the 1990s onward, several factors have contributed to the overall decline in the incidence of pseudophakic corneal edema in KSA: (1) an increasingly higher percentage of ophthalmic surgeons practicing in the Kingdom who have graduated from modern residency training programs, (2) the widespread availability of modern phacoemulsification machines, (3) the universal availability of viscoelastics in government facilities and in the private sector, and (4) the registration and monitoring of physician performance by the Saudi Council for Health Specialties. This decline in the overall incidence of pseudophakic corneal edema in KSA has coincided with what has occurred in other developed countries during the same time period.[100]

The introduction of excimer laser technology to KKESH in 1993 resulted in a substantial decrease in the number of corneal transplants performed because of corneal degenerations.[72] Between 1983 and 1992, greater than 10% of corneal transplants were performed for this indication.[72] Most of these cases were done for climatic droplet keratopathy, which is particularly common in Saudi males over the age of 50 years.[101] Fortunately, most of the pathology is in the anterior 100 μm of the cornea and is, thus, amenable to phototherapeutic keratectomy.[102] Since 1993, fewer than 2% of corneal transplants have been performed because of corneal degeneration, making it the least common indication for keratoplasty at KKESH.[72] This rate is virtually identical to the 2.6% rate of keratoplasty reported in 2002 for corneal degeneration in the United States.[100]

Initially, primary adult optical PKP accounted for almost all keratoplasty procedures at KKESH. However, there has been some demand to perform primary optical PKP in children because of a relatively high prevalence of congenital glaucoma[103] and congenital hereditary endothelial dystrophy in KSA[99] compared with Western countries. Not unexpectedly, the high volume of PKP in both adults and children has been associated with a commensurate increase in repeat PKP.[104] Today, an increasing number of candidates for PKP are being managed with lamellar procedures.[105-107] Deep anterior

lamellar keratoplasty is being performed more frequently for keratoconus and, to a lesser extent, for stromal scarring and dystrophies.[105-107] Descemet's stripping automated endothelial keratoplasty (DSAEK), which has been popularized for the management of corneal edema,[108-114] is currently being introduced in KSA for management of corneal edema. Finally, there has been an increased tendency to perform therapeutic PKP in eyes with noninfected and infected ulceration. Currently, primary adult optical PKP accounts for only slightly more than 50% of corneal transplants performed at KKESH. Inasmuch as results of pediatric, repeat, and therapeutic PKP have already been extensively reviewed and published, this dissertation focused on the outcomes of graft survival and visual acuity following primary adult optical PKP.

IV. HYPOTHESIS/ANTICIPATED RESULTS

1. Because of socioeconomic, cultural, and public health service factors present in the Kingdom of Saudi Arabia, corneal graft survival and visual outcome may be adversely affected, especially in older patients.

2. Corneal graft survival rates may be similar to those of published Western series for keratoconus and stromal dystrophy because of the predominance of patients younger than 25 and 40 years of age, respectively, for these surgical indications. Specific factors that may have an adverse impact on graft survival for eyes with keratoconus include previous episodes of hydrops and the concomitant presence of vernal keratoconjunctivitis in eyes with keratoconus.

3. Corneal graft survival rates may be lower than those of published Western series for stromal scarring (post-trachoma, microbial keratitis, trauma) and corneal edema (phakic, aphakic, pseudophakic), most of which occur in patients older than 50 years of age. Specific factors that may be associated with decreased graft survival include patient age, gender, distance from the surgical center, and postoperative visit compliance.

V. PATIENTS AND METHODS

After approval was obtained from the KKESH and University of Stellenbosch Institutional Review Boards, the medical records of every Saudi patient 12 years of age or older who underwent primary adult optical penetrating keratoplasty (PKP) at King Khaled Eye Specialist Hospital (KKESH) between January 1, 1997, and December 31, 2001, were retrospectively reviewed. Patients for whom less than 3 months' follow-up was available were excluded from the statistical analysis.

Almost all surgical procedures were performed with internationally acquired donor tissue, all of which was obtained from Eye Bank Association of America (EBAA)-accredited facilities in the United States. All tissue met EBAA minimum standards of donor age, endothelial cell density (ECD), and death-to-preservation time.[115] All tissue was recovered, processed, and maintained in Optisol-GS storage media at participating eye banks, after which it was packed into an appropriate expandable polystyrene shipping container in accordance with EBAA Procedures Manual article L2.000, and air-shipped to New York City. The container was then transported on the next available Saudi Arabian Airlines flight to Riyadh. These nonstop flights between New York City and Riyadh occurred 3 times weekly, each one lasting approximately 13 to 14 hours. The container was maintained throughout the flight at 4°C in a refrigerator located in the food preparation and storage facilities. Upon arrival at King Khaled International Airport, the container was immediately transferred from the plane to the medications refrigerator at the appropriate temperature in the cargo office. Shortly after its arrival, a KKESH representative collected the container and delivered it to the Emergency Room (ER) charge nurse at the hospital (after working hours) or to an eye bank technician (during working hours). The ER charge nurse or the eye bank technician then completed a tissue arrival check, which validated the date and time of arrival, condition of the shipping container, number and status of the ice blocks, number of donor tissue specimens, and status of each donor tissue container. At the KKESH Eye Bank, an EBAA-certified technician matched and confirmed the documentation accompanying

each tissue, reexamined and reevaluated the tissue for suitability, and placed it in the temperature-controlled eye bank refrigerator at 4°C. The tissue was removed from the refrigerator 1 to 2 hours prior to the scheduled surgical case, transferred to the operating theater, and allowed to warm to room temperature. At the time of surgery, the corneal rim was collected after trephination and sent for appropriate microbiological processing for bacterial and fungal cultures. Locally acquired tissue, when available, was harvested and processed by EBAA-certified personnel from the KKESH Eye Bank.

Upon notification of the impending arrival of tissue from the United States or from locally acquired donors, the chief eye bank technician schedules cases into specially designated operating theater slots reserved for such cases with the operating ophthalmologist. Donor tissue is randomly assigned to the ophthalmologists responsible for the scheduled cases each day. HLA and ABO histocompatibility matching is not performed, despite recent evidence that such matching may be of some benefit, even in low-risk keratoplasty.[116-118] When surgeons have more than one case, they may choose the allocation of the assigned tissue to the patients on their surgical list.

All surgeries were performed on an inpatient basis by members of the Anterior Segment Division. The selection of surgical techniques such as donor and recipient graft size and suture technique was at the discretion of the operating surgeon. Postoperatively, patients were evaluated daily until reepithelialization was complete, and then discharged from the hospital. They were usually examined 1 to 2 weeks following discharge; after 1, 3, 6, 9, 12, 18, and 24 months; and then yearly thereafter. After surgery, topical corticosteroids and antibiotics were administered in dosages at the discretion of the operating surgeon. Antibiotics were generally utilized 4 times daily throughout the inpatient stay and until the first outpatient follow-up examination. Typically, topical steroids (prednisolone acetate 1.0% or equivalent) were administered 4 to 6 times daily during hospitalization and 4 times daily for the first 3 postoperative months. They were then tapered slowly at the discretion of the attending ophthalmologists, with most ophthalmologists electing to maintain patients on topical steroids for the duration of the

first postoperative year. After 1 year, patients who were aphakic or pseudophakic and were not steroid responders were maintained on a daily drop of steroid. Because most cases in this series were not considered to be high-risk keratoplasty, very few patients received topical cyclosporine, and no patients were treated with systemic cyclosporine. Patients with presumptive herpetic eye disease were treated prophylactically with systemic antivirals on an indefinite basis. The protocol for suture removal varied among the ophthalmologists, with some physicians removing all sutures after 18 to 36 months and others selectively removing only loosened sutures or tight sutures that induced unacceptable astigmatism.

The surgical indications for primary adult optical PKP included procedures that were performed with the intention of providing improved visual acuity in a patient who was 12 years or older. The surgical indications were subclassified as keratoconus, stromal dystrophy, corneal edema, or stromal scarring. A diagnosis of keratoconus was accepted if it had been made by a member of the Anterior Segment Division on the basis of the characteristic constellation of clinical, refractive, and topographic abnormalities associated with this disorder. A diagnosis of stromal dystrophy was accepted on the basis of the characteristic clinical appearance and a postoperative histopathological confirmation of the diagnosis. Corneal edema included all cases of phakic corneal edema, as well as aphakic and pseudophakic corneal edema. Stromal scarring included acquired stromal opacities of any etiology, including trauma and previous trachomatous, bacterial, fungal, or herpetic keratitis.

Risk factors that were selected for inclusion in the statistical analysis were classified as demographic variables, donor tissue variables, surgical variables, and postoperative complications. Demographic factors that were analyzed included gender, age, region of residence, compliance with scheduled office visits, and unscheduled visits to the Emergency Room (ER) at KKESH. The region of residence was classified as either central region, which was within driving distance of the hospital, or non-central region, which required air transportation to and from visits. Compliance with scheduled office

visits was recorded as a percentage of scheduled visits kept by the patient. Donor tissue variables included donor age, ECD (cells/mm^2), death-to-preservation time, and preservation-to-surgery time. Surgical variables included graft size and suture technique, as well as previous, concomitant, or subsequent ipsilateral cataract or glaucoma procedures. Postoperative complications that were identified and extracted from the medical records included primary graft failure, endothelial rejection episodes, glaucoma worsening, bacterial keratitis, endophthalmitis, persistent epithelial defect (PED), and wound dehiscence. The statistical analysis included complications that occurred at any time between PKP and the most recent visit in eyes without graft failure, as well as those that occurred between PKP and the documented date of that irreversible edema in eyes with graft failure. Complications that occurred after graft failure were not included in the statistical analysis. Complications were enumerated by the number of eyes that experienced each complication, even if more than one episode of the same complication occurred in the same eye (eg, endothelial rejection episodes). Because it is not always possible to correlate directly multifactorial graft failure with the occurrence of a specific complication, statistical analysis was performed to evaluate the complication-associated risks of graft failure for occurrence of individual or multiple complications.

Primary graft failure was defined as corneal edema that was present from the time of PKP and did not clear after 8 weeks and for which there were no known operative or postoperative complications or underlying recipient conditions that would explain the biological dysfunction.[115] Endothelial rejection episodes were identified using the definition put forth by the Collaborative Corneal Transplantation Studies Research Group[119] and included one or more of the following: new onset graft edema, an endothelial rejection line, more than 5 keratic precipitates, or increased number of aqueous cells. Preexisting glaucoma was defined as any surgical procedure performed for intraocular pressure (IOP) control or the need to use 1 or more IOP-lowering medications to obtain a satisfactory IOP, as determined by the treating ophthalmologist. Glaucoma worsening was defined as the postoperative need to do one of the following: (1) to perform surgical intervention to control IOP, (2) to institute glaucoma medications

in an eye without preexisting glaucoma, or (3) to increase the number of glaucoma medications required in an eye with preexisting glaucoma. To fulfill one of these definitions of medical worsening, the increased use or new onset use of glaucoma medications had to be either (1) on a sustained basis (≥3 consecutive postoperative clinic visits) or (2) in use at the time of the most recent postoperative visit. Cases of transient postoperative increase in IOP and reversible steroid-induced glaucoma were not included in the statistical analysis if they did not meet the requirement for sustained use of glaucoma medication. The target level for optimal IOP control was defined by the treating consultant and varied because of a number of factors, including the degree of glaucomatous optic atrophy and visual field loss, as well as physician preference. Accordingly, the diagnosis of glaucoma escalation was exclusively established on the surgical intervention or medication prescribing pattern of the treating physician rather than on the actual IOP. A diagnosis of bacterial keratitis was based on positive cultures, as defined by confluent growth at the site of inoculation on one solid medium or growth of the same organism in two or more media. A diagnosis of endophthalmitis required characteristic clinical findings and a positive aqueous or vitreous culture. A PED was any epithelial defect that occurred after initial reepithelialization and lasted more than 14 days, exclusive of those which occurred during the resolution of bacterial keratitis. Wound dehiscence was any disruption of the surgical wound that was sufficient to require the reintroduction of sutures.

Outcome measures were graft clarity and visual acuity. Because serial pachymetry and endothelial cell measurements were not available, an absolute determination was made in each case of either a clear or failed graft. Graft failure was strictly defined as irreversible loss of central graft clarity, irrespective of the level of vision. For statistical calculations, exact surgical dates and follow-up dates were recorded. For grafts which remained clear, the follow-up interval was the time between the surgical procedure and the most recent examination. For grafts that failed, the follow-up interval was the time between the surgical procedure and the first examination at which irreversible loss of

graft clarity was documented. Mean follow-up calculations were based on the duration between surgery and the most recent visit for clear grafts.

The best corrected visual acuity (BCVA) was defined as the best vision obtained with spectacles, contact lens, or refraction. In the event that only the uncorrected visual acuity was available, it was recorded as the BCVA for purposes of statistical analysis. For each eye, the best corrected vision at the time of the most recent examination was the endpoint. If a repeat PKP was performed, the final vision for the initial graft was recorded as the vision obtained just prior to repeat keratoplasty.

All data were entered onto a Microsoft (Redmond, WA, USA) Excel spreadsheet and analyzed using Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, North Carolina, USA). Graft survival probability was calculated using the standard Kaplan-Meier method and life table method. Comparisons between groups were performed with Wilcoxon log-rank sum tests. Calculations of hazard ratios (HRs) associated with demographic variables, donor tissue variables, surgical variables, and complications were initially performed with univariate Cox proportional hazard regression analysis and the Wald chi-square test. The risk of a variable being associated with graft failure was expressed as an HR with a 95% confidence interval (CI). Variables that were statistically significant on univariate analysis were further analyzed with multivariate Cox proportional hazard regression analysis and the Wald chi-square test. Simple comparisons between categorical variables were performed with the Fisher exact test or the chi-square test. The term *significance* was accepted if the *P* value was less than 0.05.

VI. RESULTS

Between January 1, 1997, and December 31, 2001, a total of 1952 keratoplasties (1721 PKPs; 231 LKPs) were performed at KKESH. Of the 1721 PKPs, there were 1468 primary PKPs and 253 repeat PKPs. Among the primary PKPs, 1385 were performed in adult patients and 83 in children. The primary adult PKPs included 969 that were carried out for optical indications and 416 that were conducted for therapeutic indications. Among the primary adult optical PKPs, 933 were performed on Saudi patients. Of these, 910 (97.5%) PKPs that were performed on 855 patients met the follow-up criteria and were included in the statistical analysis (Table 1).

Among the 910 eyes with primary adult optical PKP that met the follow-up criteria, there were 464 eyes (439 patients) with keratoconus, 188 eyes (181 patients) with corneal edema, 175 eyes (161 patients) with stromal scarring, and 83 eyes (74 patients) with stromal dystrophy. A history of vernal keratoconjunctivitis (VKC) was present in 80 eyes with keratoconus. Among eyes with corneal edema, there were 92 eyes with pseudophakic corneal edema (66 associated with posterior chamber intraocular lenses [PC IOLs]; 26 anterior chamber intraocular lenses [AC IOLs]), 63 eyes with aphakic corneal edema, and 33 eyes with phakic corneal edema, most of which were Fuchs' endothelial dystrophy. Among eyes with stromal scarring, there were 127 eyes with post-trachomatous scarring, 10 with previous trauma, 9 with previous microbial keratitis (8 bacterial, 1 fungal), and 29 with undetermined etiology, most of which were presumed to have been caused by *Herpes simplex* virus. All eyes with stromal dystrophy had a histopathologic diagnosis of macular stromal dystrophy.

Male patients accounted for 536 (58.9%) of the total cases. There were more male patients among the eyes with keratoconus (61.0%), corneal edema (60.1%), stromal scarring (54.9%), and stromal dystrophy (53.0%).

There were statistically significant differences in patient age among the surgical indications (P <0.001). Patients with keratoconus were the youngest (mean age = 22.7 years), whereas patients with corneal edema were the oldest (mean age = 65.5 years).

Among eyes with keratoconus, those with concomitant VKC were younger than those in whom this diagnosis was not present (20.2 years vs 23.2 years, respectively; P = 0.02). Patients with both corneal edema and stromal scarring had a mean age that was greater than 60 years. There was little variation in the mean age of patients with different categories of corneal edema. However, there was a 2-decade range among the categories of stromal scarring, with those attributed to trauma being the youngest (mean age = 44.4 years) and those with post-trachomatous scarring being the oldest (mean age = 64.7 years).

There were statistically significant differences in mean follow-up of clear grafts among the surgical indications (P<0.001), ranging from 57.8 months for eyes with keratoconus to 33.5 months for eyes with corneal edema (Table 2). Complete follow-up data (clear grafts under observation + failed grafts) were available for at least 5 years in 59.0% of eyes with stromal dystrophy, 55.9% with corneal edema, 52.8% with keratoconus, and 45.1% with stromal scarring.

Table 1. Primary Adult Optical Penetrating Keratoplasty: Demographics

	n			Age, y
	All	Male	Female	Mean (Range)
Keratoconus				
Without VKC	384	233	151	23.2 (12-78)
With VKC	80	50	30	20.2 (13-31)
All	464	283	181	22.7 (12-78)
Corneal edema				
Phakic	33	18	15	67.2 (46-93)
ACE	63	38	25	65.6 (29-65)
PCE (PC IOL)	66	41	25	65.1 (37-90)
PCE (AC IOL)	26	16	10	63.8 (39-77)
All	188	113	75	65.5 (29-65)
Stromal scarring				
Trachoma	127	61	66	64.7 (40-90)
Microbial keratitis	9	5	4	54.4 (16-83)
Trauma	10	6	4	44.4 (19-67)
Other	29	24	5	57.6 (33-92)
All	175	96	79	61.8 (16-92)
Stromal dystrophy				
Macular dystrophy	83	44	39	34.2 (19-77)
Total	910	536	374	40.1 (12-95)

VKC = vernal keratoconjunctivitis; ACE = aphakic corneal edema; PCE = pseudophakic corneal edema; PC IOL = posterior chamber intraocular lens; AC IOL = anterior chamber intraocular lens.

Table 2. Primary Adult Optical Penetrating Keratoplasty: Follow-Up

	Eyes With Complete Follow-up, %[1]			Follow-up, mo Mean (Range)[2]
	1 year	3 years	5 years	
Keratoconus	97.8	78.9	52.8	57.8 (3.0-127.4)
Corneal edema	89.9	68.6	55.9	33.5 (4.0-117.4)
Stromal scarring	88.6	60.0	45.1	41.0 (3.0-112.6)
Stromal dystrophy	95.2	73.5	59.0	55.7 (4.9-111.7)
Total	94.2	73.6	52.5	51.5 (3.0-127.4)

[1] Clear grafts under observation + failed grafts
[2] Clear grafts only

Graft Survival

For the entire study group, the probability of graft survival was 96.7% at 1 year, 86.2% at 3 years, and 80.9% at 5 years (Table 3, Figure 1). Overall, clear grafts were present in 83.2% of eyes at the most recent examination after a mean follow-up of 51.5 months.

The probability of graft survival differed significantly among the surgical indications at all time points between 1 and 5 years ($P < 0.001$) (Figure 2). The results were best in eyes with keratoconus, followed by stromal dystrophy, stromal scarring, and corneal edema. The least variation occurred in the first year when survival ranged from 98.9% for keratoconus to 91.6% for corneal edema. This gap progressively increased until the fifth year when graft survival probability was 96.1% for keratoconus and 40.3% for corneal edema. Overall, 96.1% of eyes with keratoconus (mean follow-up = 57.8 months), 85.5% with stromal dystrophy (mean follow-up = 55.7 months), 77.1% with stromal scarring (mean follow-up = 41.0 months), and 55.9% with corneal edema (mean follow-up = 33.5 months) were clear at the most recent examination.

In eyes with keratoconus, graft survival probability was 98.9% at 1 year, 98.0% at 3 years, and 96.1% at 5 years (Figure 3). This category had the best probability of graft survival at all time points. At 5 years, graft survival probability was 97.3% in eyes with VKC and 95.3% in eyes without VKC ($P = 0.506$) (Figure 4). Previous hydrops was not significantly associated with an increased risk of graft failure in eyes with or without VKC ($P = 0.29$).

Graft survival probability in eyes with corneal edema was 91.6% at 1 year, 58.7% at 3 years, and 40.3% at 5 years (Figure 5). This category had the worst probability of graft survival at all time points. The 5-year survival probability was 33.3% for eyes with phakic corneal edema, 38.2% for aphakic corneal edema, 49.6% for pseudophakic corneal edema with PC IOLs, and 24.1% for pseudophakic corneal edema with AC IOLs (Figure 6). There were no significant differences in survival probability between eyes

with phakic corneal edema and those with aphakic or pseudophakic corneal edema (*P*= 0.758).

In eyes with stromal scarring, graft survival probability was 96.9% at 1 year, 79.4% at 3 years, and 71.1% at 5 years (Figure 7). At 5 years, survival probability was 76.6% for eyes in which the etiology for the stromal opacity was trachoma, 64.3% for previous microbial keratitis, 80.0% for previous trauma, and 49.1% for other (mostly presumed herpetic) etiologies (*P* = 0.001) (Figure 8).

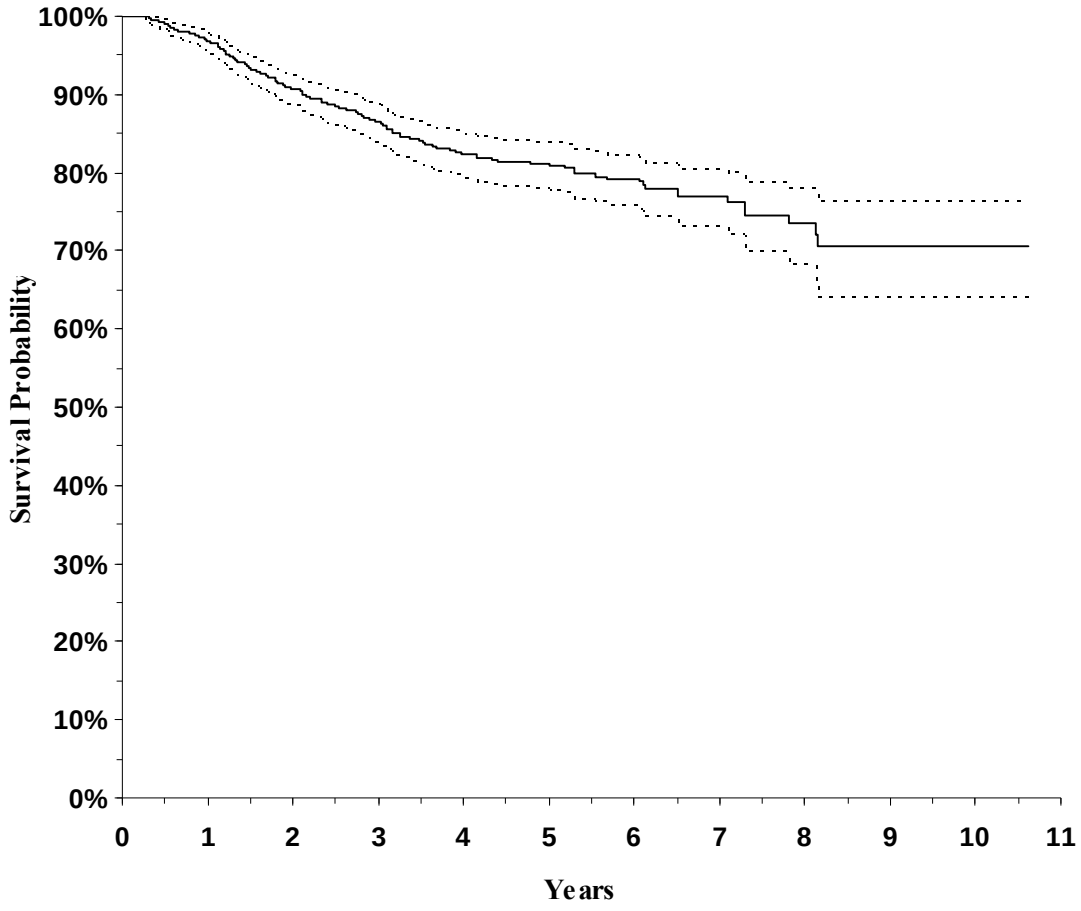
Graft survival probability in eyes with stromal dystrophy was 96.4% at 1 year, 87.6% at 3 years, and 85.9% at 5 years (Figure 9). This category had the second best probability of graft survival at all time points.

Table 3. Primary Adult Optical Penetrating Keratoplasty: Graft Survival Probability vs Surgical Indication

	All	Keratoconus	Corneal Edema	Stromal Scarring	Stromal Dystrophy	*P* Value[1]
Eyes, n	910	464	188	175	83	
Clear grafts						
n	757	446	105	135	71	<0.001
%	83.2	96.1	55.9	77.1	85.5	
Graft survival probability, % (95% CI)						
1 year	96.7 (95.5, 97.8)	98.9 (97.4, 99.5)	91.6 (86.4, 94.8)	96.9 (92.6, 98.7)	96.4 (89.1, 98.8)	<0.001
2 years	90.4 (88.1, 92.2)	98.5 (96.8, 99.3)	72.6 (64.8, 78.9)	86.0 (79.2, 90.8)	90.8 (81.6, 95.5)	<0.001
3 years	86.2 (83.5, 88.4)	98.0 (96.1, 98.9)	58.7 (50.0, 66.4)	79.4 (71.3, 85.5)	87.6 (77.4, 93.4)	<0.001
4 years	82.2 (79.1, 84.8)	96.4 (94.0, 97.9)	44.7 (35.2, 53.8)	73.8 (64.6, 80.9)	85.9 (75.3, 92.2)	<0.001
5 years	80.9 (77.8, 83.7)	96.1 (93.5, 97.6)	40.3 (30.5, 49.8)	71.1 (61.4, 78.7)	85.9 (75.3, 92.2)	<0.001

CI = confidence interval.
[1]Wilcoxon log-rank sum test.

Figure 1. Graft Survival Probability: All Indications

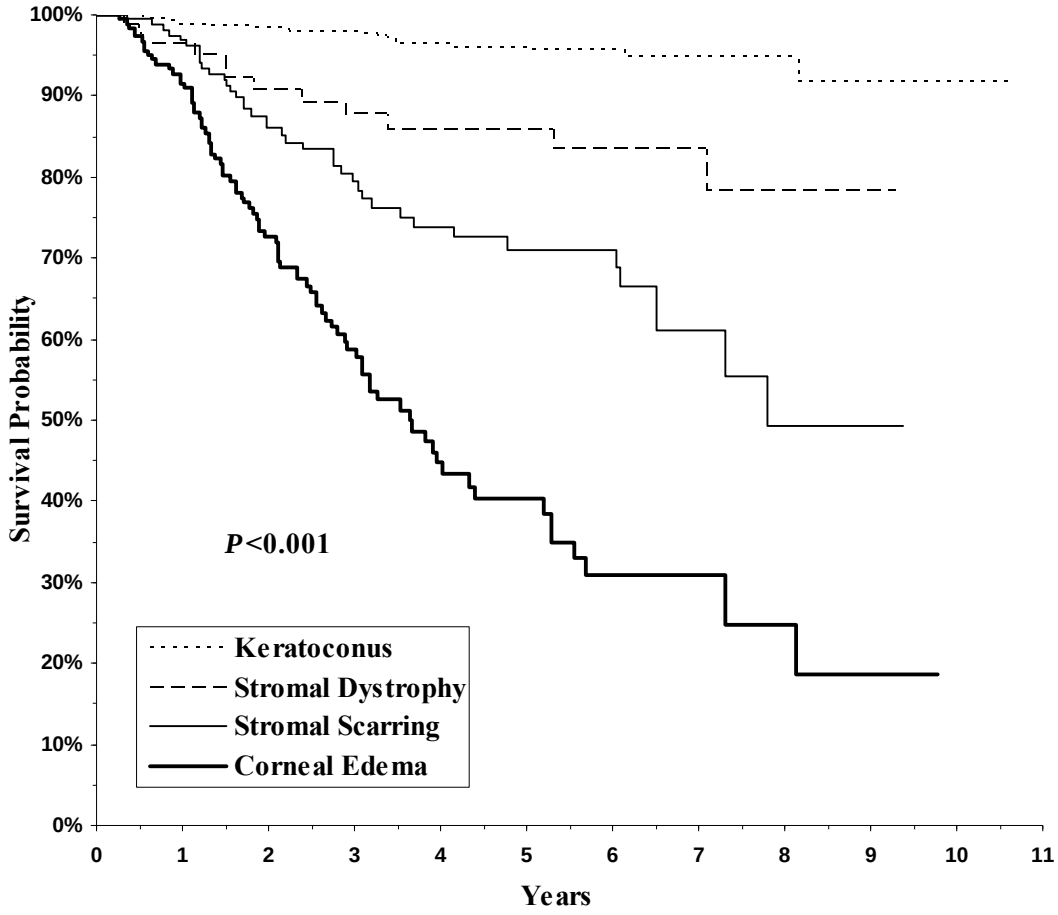


All indications (N = 910; clear grafts under observation at 1, 3, and 5 years = 702, 505, and 324, respectively).

Solid line = 50% probability estimate

Dashed line = 95% confidence interval

Figure 2. Graft Survival Probability vs Surgical Indication



P-value = Wilcoxon log-rank sum test.

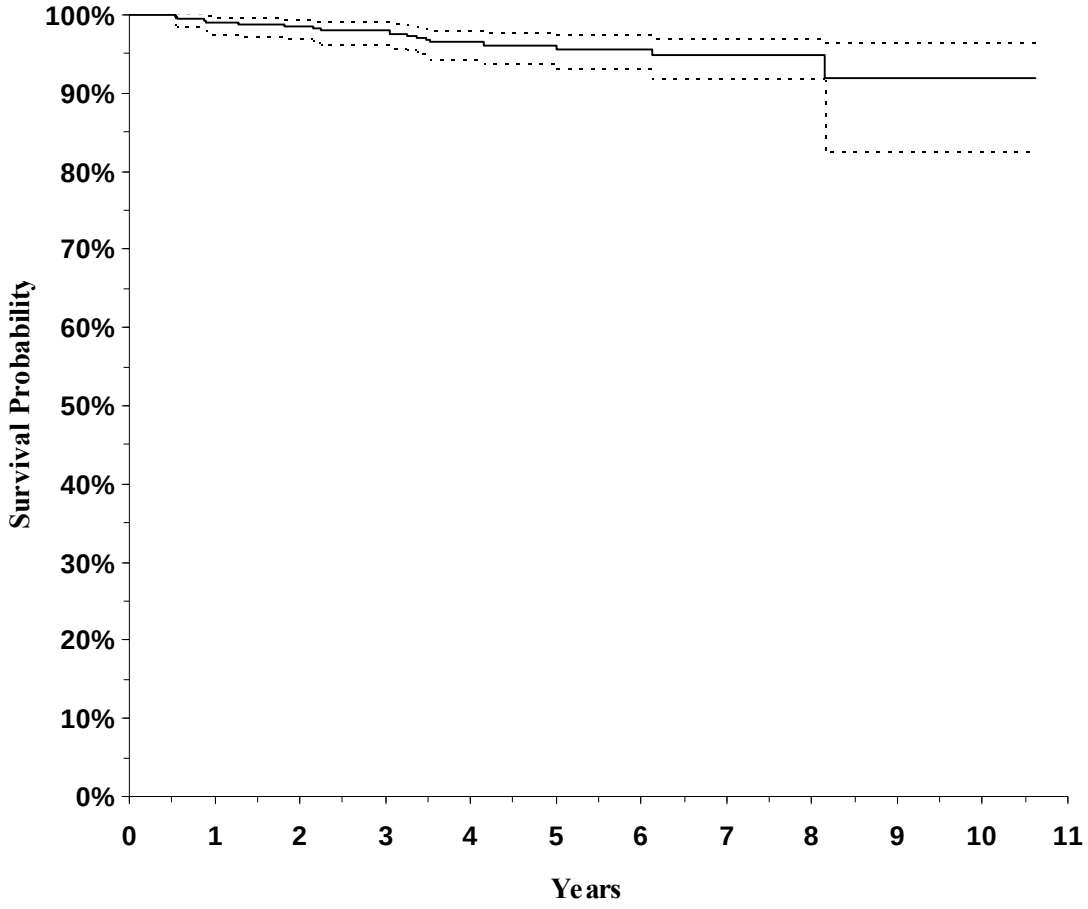
Keratoconus (n = 464; clear grafts under observation at 1, 3, and 5 years = 436, 354, and 234, respectively).

Stromal dystrophy (n = 83; clear grafts under observation at 1, 3, and 5 years = 68, 49, and 37, respectively).

Stromal scarring (n = 175; clear grafts under observation at 1, 3, and 5 years = 112, 62, and 36, respectively).

Corneal edema (n = 188; clear grafts under observation at 1, 3, and 5 years = 86, 40, and 17, respectively).

Figure 3. Graft Survival Probability: Keratoconus

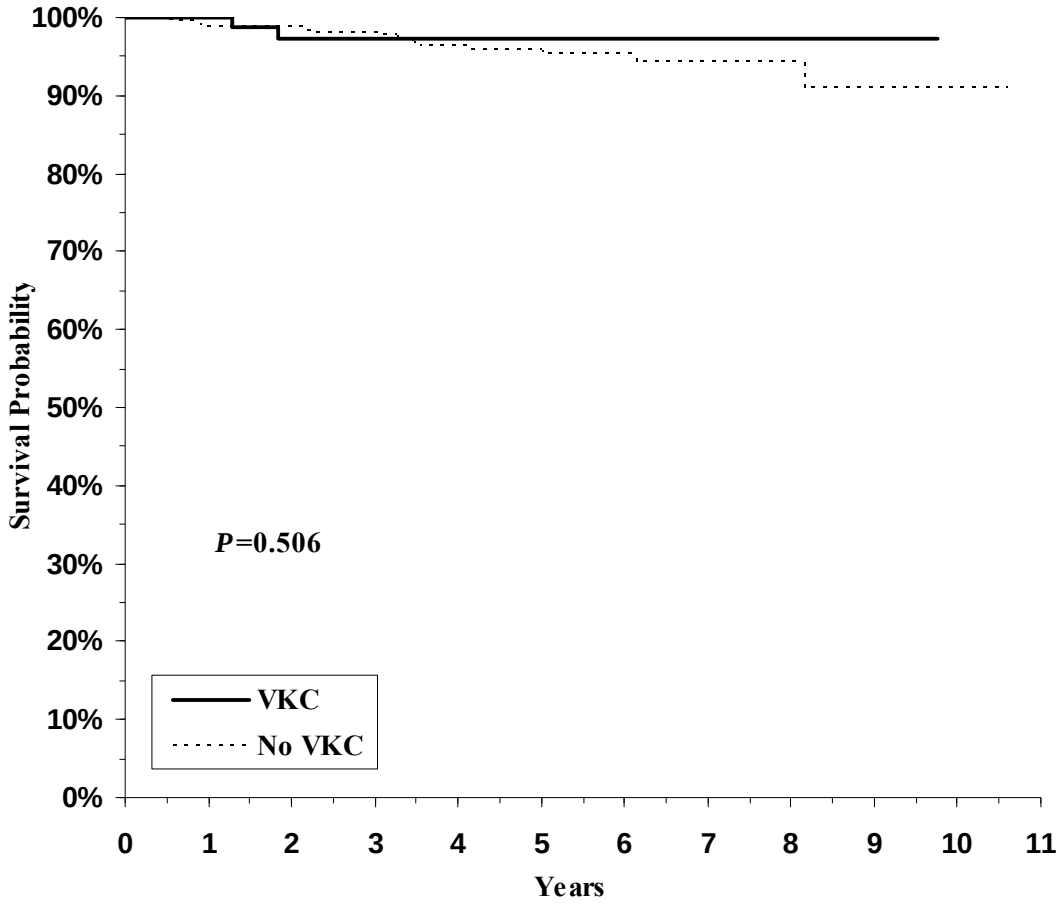


Keratoconus (n = 464; clear grafts under observation at 1, 3, and 5 years = 436, 354, and 234, respectively).

Solid line = 50% probability estimate

Dashed line = 95% confidence interval

Figure 4. Penetrating Keratoplasty for Keratoconus: Graft Survival Probability vs Presence or Absence of Vernal Keratoconjunctivitis (VKC)

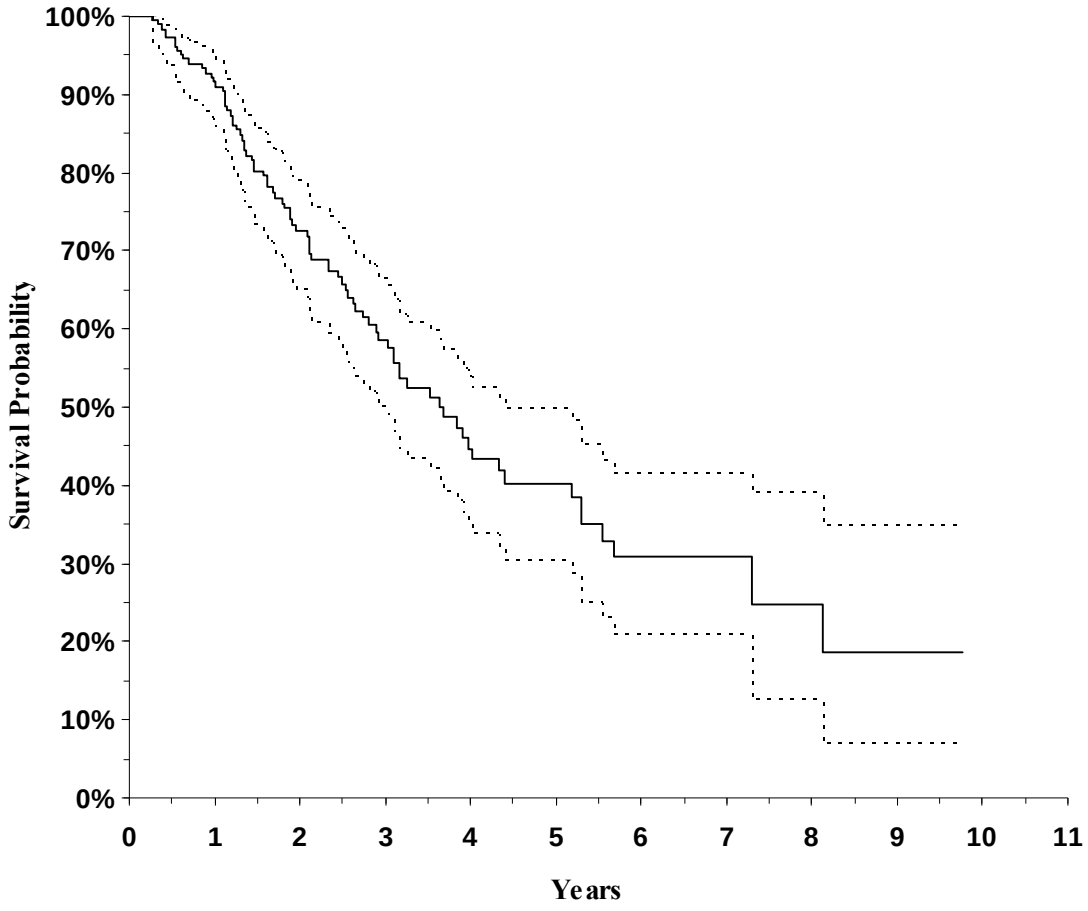


P-value = Wilcoxon log-rank sum test.

VKC (n = 80; clear grafts under observation at 1, 3, and 5 years = 77, 62, and 39, respectively).

No VKC (n = 384; clear grafts under observation at 1, 3, and 5 years = 359, 292, 195, respectively).

Figure 5. Graft Survival Probability: Corneal Edema

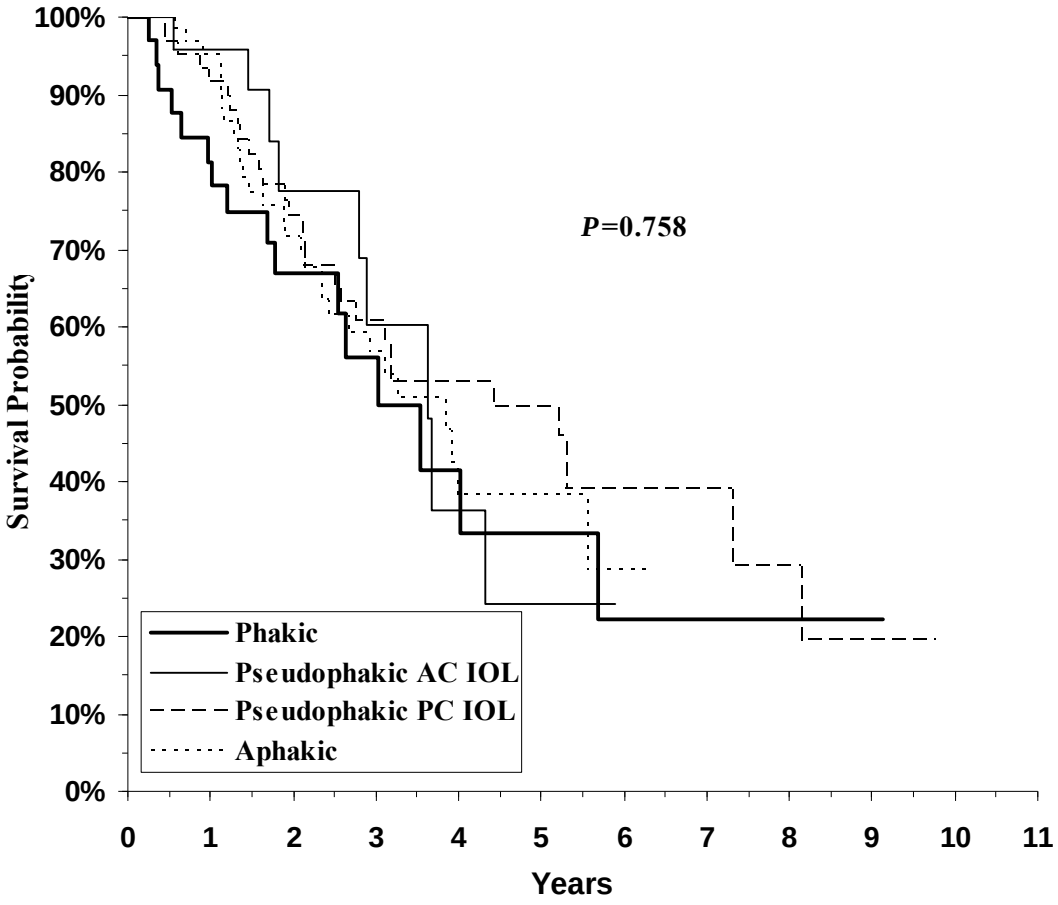


Corneal edema (n = 188; clear grafts under observation at 1, 3, and 5 years = 86, 40, and 17, respectively).

Solid line = 50% probability estimate

Dashed line = 95% confidence interval

Figure 6. Penetrating Keratoplasty for Corneal Edema: Graft Survival Probability vs Lens Status



P-value = Wilcoxon log-rank sum test.

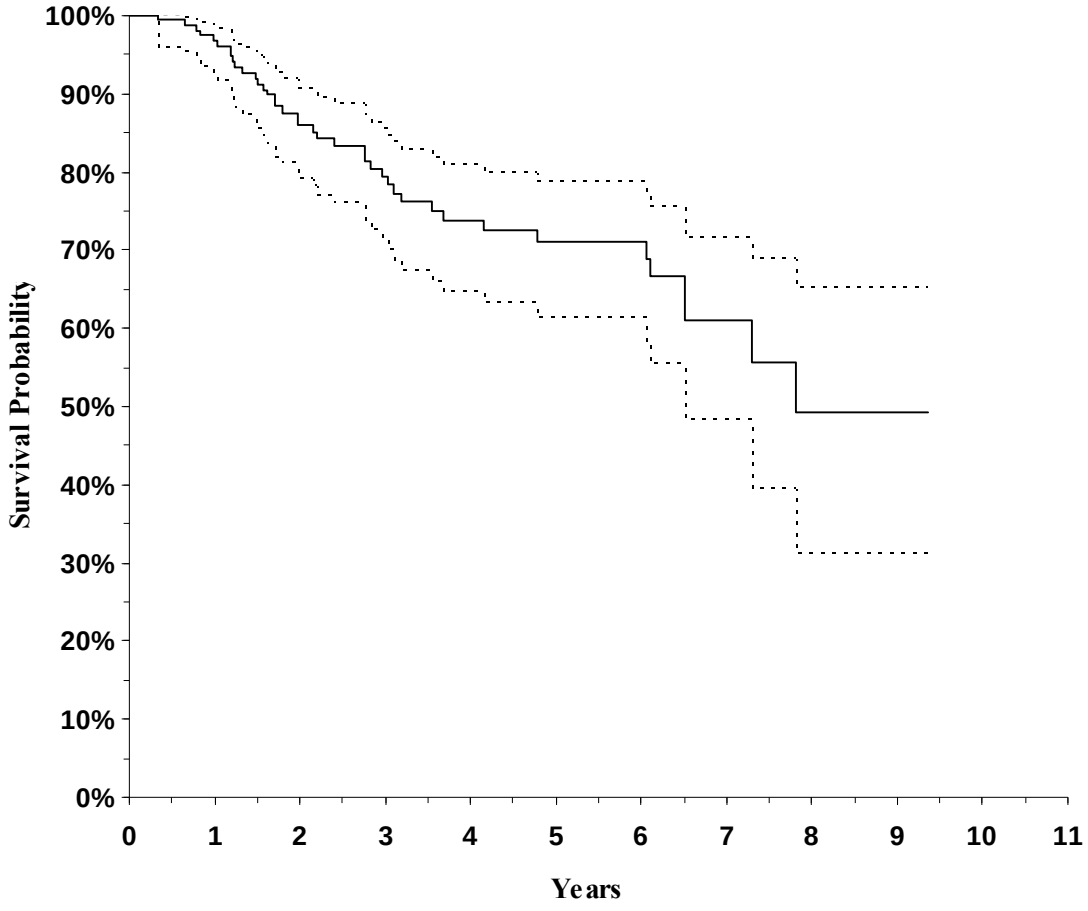
Phakic corneal edema (n = 33; clear grafts under observation at 1, 3, and 5 years = 16, 6, and 2, respectively).

Pseudophakic corneal edema with anterior chamber intraocular lens (AC IOL) (n = 26; clear grafts under observation at 1, 3, and 5 years = 11, 8, and 1, respectively).

Pseudophakic corneal edema with posterior chamber intraocular lens (PC IOL) (n = 66; clear grafts under observation at 1, 3, and 5 years = 37, 17, and 8, respectively).

Aphakic corneal edema (n = 63; clear grafts under observation at 1, 3, and 5 years = 22, 9, and 6, respectively).

Figure 7. Graft Survival Probability: Stromal Scarring

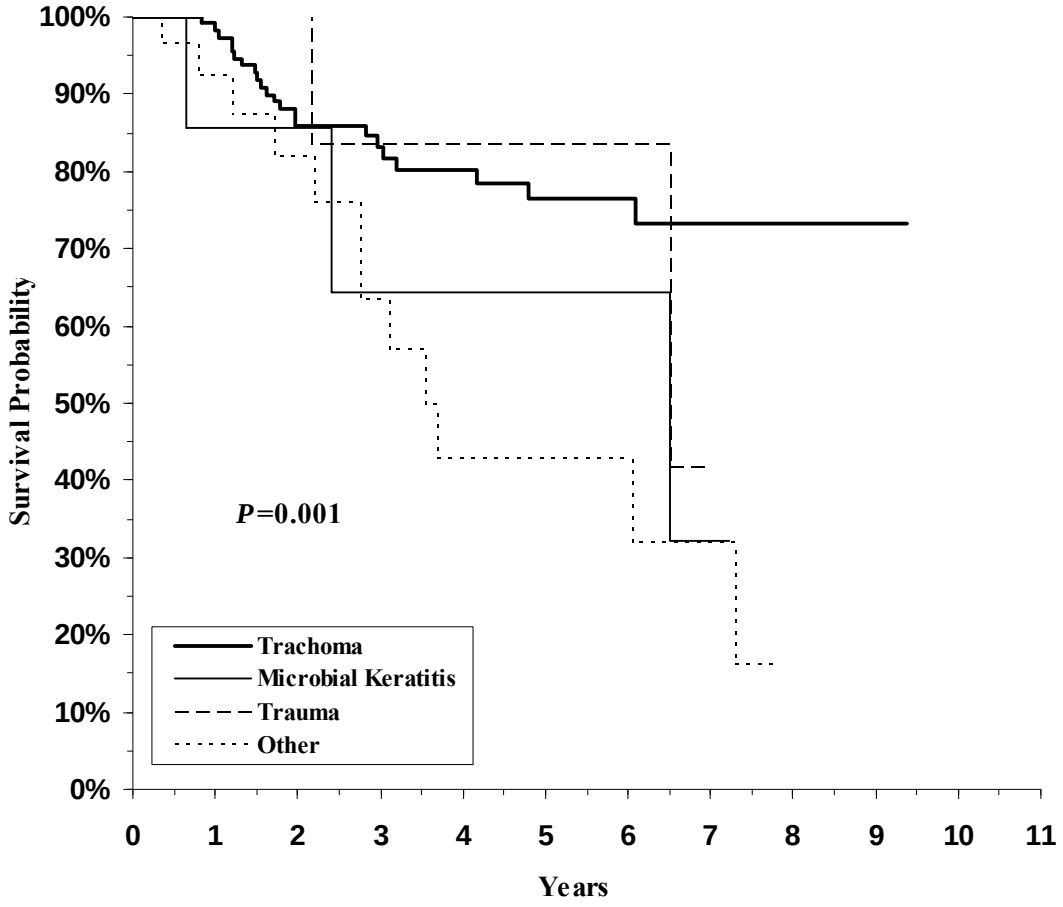


Stromal scarring (n = 175; clear grafts under observation at 1, 3, and 5 years = 112, 62, and 36, respectively).

Solid line = 50% probability estimate

Dashed line = 95% confidence interval

Figure 8. Penetrating Keratoplasty for Stromal Scarring: Graft Survival Probability vs Etiology



P-value = Wilcoxon log-rank sum test.

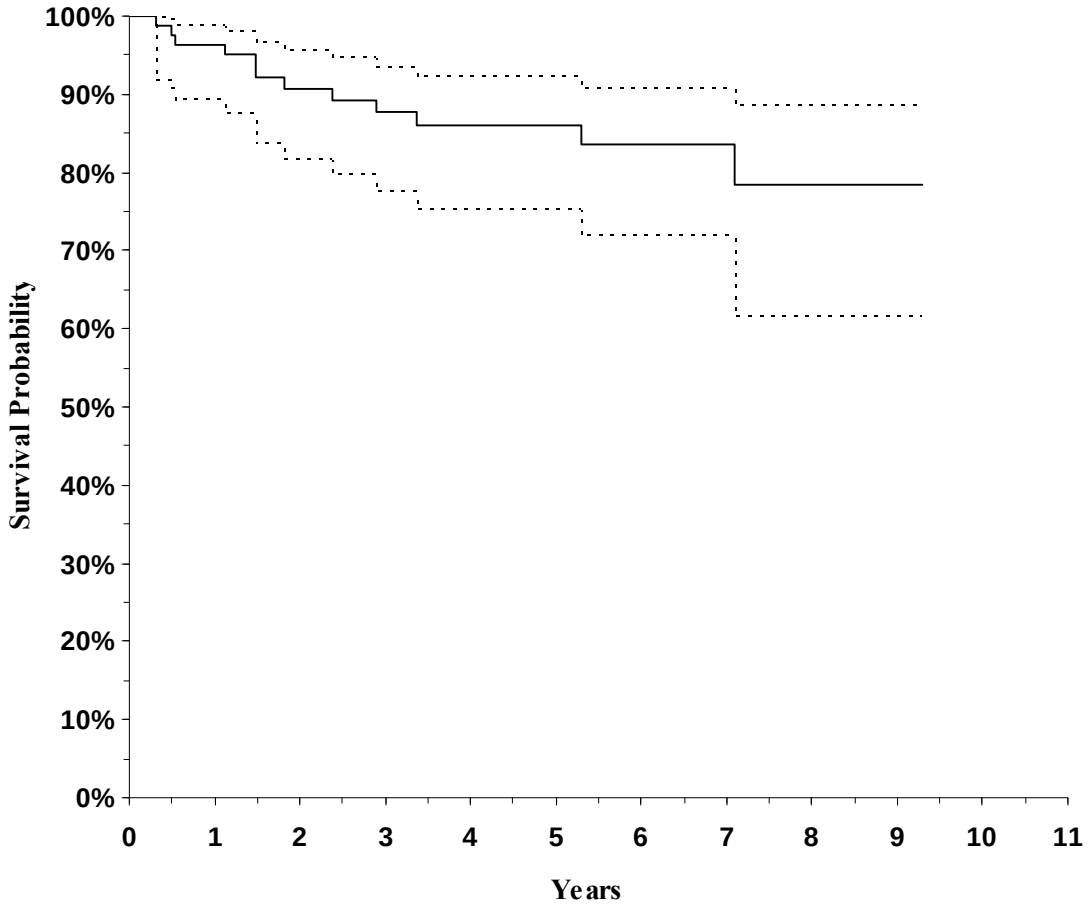
Trachoma (n = 127; clear grafts under observation at 1, 3, and 5 years = 92, 52, and 32, respectively).

Microbial keratitis (n = 9; clear grafts under observation at 1, 3, and 5 years = 4, 2, and 1, respectively).

Trauma (n = 9; clear grafts under observation at 1, 3, and 5 years = 7, 4, and 2, respectively).

Other (n = 29; clear grafts under observation at 1, 3, and 5 years = 9, 4, and 1, respectively).

Figure 9. Graft Survival Probability: Stromal Dystrophy



Stromal dystrophy (n = 83; clear grafts under observation at 1, 3, and 5 years = 68, 49, and 37, respectively).

Solid line = 50% probability estimate

Dashed line = 95% confidence interval

Country-specific Risk Factors vs Graft Survival

The impact of country-specific factors is summarized in Table 4. Increasing donor tissue age was the only variable that was significantly associated with an increased risk of graft failure on both univariate and multivariate analyses.

Table 4. Primary Optical Adult Penetrating Keratoplasty: Risk Factors vs Graft Survival Probability

Variable	HR[1] (95% CI)	*P* Value[1]	*P* Value[2]
Demographic variables			
Gender	1.04 (0.76, 1.43)	0.817	
Region	1.06 (0.76, 1.43)	0.716	
Visit compliance	0.95 (0.84, 1.06)	0.355	
Donor tissue variables			
Donor age	1.24 (1.13, 1.36)	0.009	0.005
Endothelial cell count	0.96 (0.91, 1.01)	0.102	
Death-to-preservation	1.02 (0.97, 1.08)	0.417	
Preservation-to-surgery	0.99 (0.98, 1.02)	0.943	

HR = hazard ratio; CI = confidence interval.
[1] Univariate Cox proportional hazard regression/Wald chi-square test.
[2] Multivariate Cox proportional hazard regression/Wald chi-square test.

Demographic Variables

Gender, region of residence, and visit compliance were not significantly associated with an increased risk of graft failure.

Graft survival probability was slightly better for women than men. The probability of graft survival for women was 97.5%, 87.0%, and 81.2% at 1 year, 3 years, and 5 years, respectively, compared with 96.4%, 85.6%, and 80.6% in men. The probability of graft survival was slightly better for non-central region patients than for those from the central region.

The probability of graft survival for non-central region patients was 97.3%, 86.2%, and 81.7% at 1 year, 3 years, and 5 years, respectively, compared with 96.5%, 86.2%, and 80.0% for central region patients.

Graft survival probability for the 100% visit compliant patients was 96.5%, 85.0%, and 79.1% at 1 year, 3 years, and 5 years, respectively, compared with 94.3%, 83.1%, and 75.6% for the least compliant patients.

A higher percentage of women kept 100% of scheduled visits than men (46.5% vs 43.9%, respectively; $P = 0.46$), whereas more men kept less than 80% of scheduled visits (18.5% vs 17.4%, respectively; $P = 0.72$). Women who lived outside the central region were significantly more likely to attend less than 80% of scheduled visits than those who lived in the central region (20.0% vs 13.6%, respectively; $P = 0.04$).

A higher percentage of patients 60 years of age or older kept 100% of scheduled visits than their younger counterparts (46.3% vs 43.5%, respectively; $P = 0.30$), but they also kept less than 80% of scheduled visits (19.0% vs 17.4%, respectively; $P = 0.54$). Fewer older patients who lived outside the central region kept less than 80% of their scheduled appointments than those who lived in the central region (22.4% vs 16.3%, respectively; $P = 0.18$).

Unscheduled follow-up examinations for 570 (62.6%) eyes were performed in the ER at KKESH. Overall, there were 1 to 4 unscheduled visits associated with 328 (36.0%) eyes, 5 to 9 for 139 (15.3%) eyes, and 10 or more for 103 (11.3%) eyes. A greater percentage of patients residing in the central region presented to the ER for 1 or more unscheduled visits (65.3% vs 60.3%, respectively), but this difference was not statistically significant ($P = 0.12$). A higher percentage of women were seen in the ER than men (64.4% vs 61.4%, respectively), but this difference was not statistically significant ($P = 0.37$). No statistics were available on the frequency or number of unscheduled patient visits at regional medical centers.

There was a significant reduction in overall graft survival among patients who presented to the ER for 1 or more unscheduled visits compared with patients who attended only scheduled postoperative appointments (81.2% vs 86.5%, respectively; P = 0.04). Furthermore, there was a reduction in graft survival in every surgical category for patients who required unscheduled examinations in the ER compared with those who did not. This difference was statistically significant for eyes with keratoconus (95.1% vs 98.1%, respectively; P<0.001) and corneal edema (49.5% vs 64.9%, respectively; P = 0.05) but not for eyes with stromal scarring (73.3% vs 82.4%, respectively; P = 0.20) or stromal dystrophy (82.0% vs 90.9%, respectively; P = 0.87).

Donor Tissue Variables

Donor tissue obtained from the United States was used for 885 (97.3%) PKPs. Locally obtained tissue was used for 25 (2.7%) PKPs, including 11 eyes with keratoconus, 8 eyes with corneal edema, 4 eyes with stromal scarring, and 2 eyes with stromal dystrophy.

The mean and median donor ages were 53.0 and 55 (range, 3-72) years, respectively. The mean ECD was 2714 (range, 2000-4449) cells/mm^2. The mean death-to-preservation time was 6 hours and 24 minutes (range, 0:15-15:00), and the mean preservation-to-surgery time was 213.0 (range, 37-353) hours.

An age-related bias existed in the distribution of donor tissue among the surgical indication groups but not between male and female patients. Donor age was significantly lower in graft recipients with a diagnosis of keratoconus (median = 53 years) or stromal dystrophy (median = 55 years) in comparison to those with corneal edema (median = 59 years) or stromal scarring (median = 59 years) (P<0.001). Although there was a bias toward older donor tissue being utilized for eyes with corneal edema and stromal scarring, these patients received donor tissue with a mean age that was 6.5 years and 2.8 years younger than the recipient, respectively. In comparison, mean donor age exceeded

that of keratoconus patients and stromal dystrophy patients by 16.3 years and 16.0 years, respectively.

Within each surgical category, however, there did not appear to be any bias with respect to matching of donor and recipient age. There was no significant correlation between donor age and recipient age within the surgical categories of keratoconus (Spearman rank correlation [r] = 0.05; P = 0.275), corneal edema (r = 0.04; P = 0.423), stromal scarring, (r = 0.12; P = 0.128), or stromal dystrophy (r = 0.03; P = 0.789).

The risk of graft failure was significantly higher for recipients of tissue from older donors on both univariate and multivariate analyses (P = 0.009, P = 0.005, respectively). The adverse impact of increasing age was especially pronounced if the donor age was 60 years or older (Figure 10). Graft survival probability with tissue from donors 60 years of age or older was 94.7% at 1 year, but it dropped to 77.4% at 3 years and to 69.1% at 5 years. In contrast, the probability of graft survival was 99.4%, 93.9%, and 91.9% at 1, 3, and 5 years, respectively, using tissue that was less than 45 years of age.

Among the surgical groups, increasing donor age was associated with a significantly increased risk of graft failure in eyes with corneal edema (HR = 1.22; 95% CI = 1.07, 1.40; P = 0.004). Although not statistically significant, the HR associated with increasing donor age was greater than 1.0 for eyes with stromal dystrophy (HR = 1.16; 95% CI = 0.91, 1.49; P = 0.234), stromal scarring (HR = 1.09; 95% CI = 0.94, 1.27; P = 0.243), and keratoconus (HR = 1.05; 95% CI = 0.90, 1.21; P = 0.554).

Increasing death-to-preservation time, preservation-to-surgery time, and ECD were not significantly associated with an increased risk of graft failure at any time interval, although slight differences in the probability of graft survival were observed at the extremes of these donor variables. The 5-year graft survival probability was slightly better when tissue with more than 2900 cells/mm^2 was utilized compared to tissue with less than 2500 cells/mm^2 (82.6% vs 78.7%, respectively). Donor tissue with death-to-preservation times that were less than 5 hours was associated with a slightly better 5-

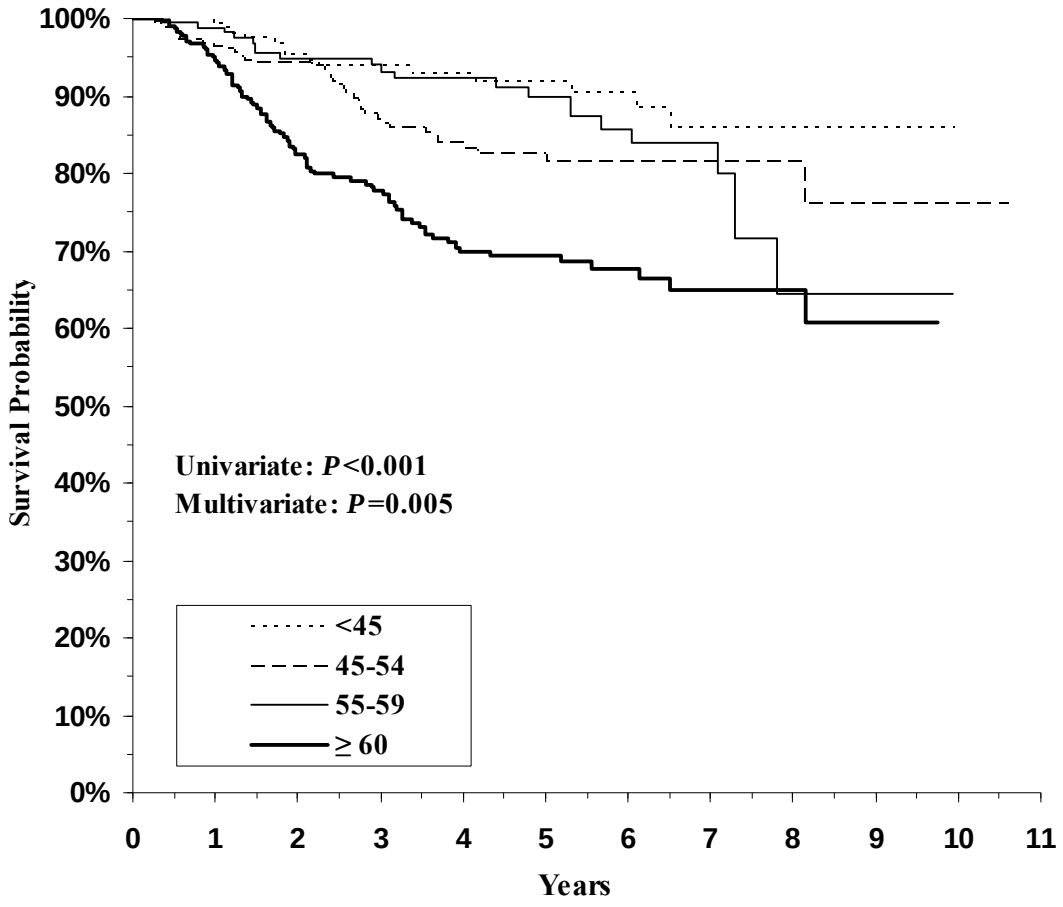
year probability of graft survival than that with more than 9 hours (82.8% vs 78.5%, respectively). Donor tissue with preservation-to-surgery times that were less than 175 hours was also associated with a slightly better 5-year graft survival probability than times that were greater than 245 hours (81.9% vs 77.3%, respectively).

Donor rim cultures were obtained in 100% of cases. Positive bacterial cultures were obtained in 177 (19.5%) donor rims. In comparison, positive fungal cultures were obtained in 6 (0.7%) donor rims. No cases of early bacterial keratitis in eyes with or without positive donor rim cultures were detected. There were no cases of early or late fungal keratitis. There were no cases of endophthalmitis associated with contaminated donor tissue.

Primary graft failure was diagnosed in 1 (0.1%) eye. This failure occurred in a 40-year-old woman with macular corneal dystrophy who had received internationally acquired tissue from a 60-year-old donor with an ECD of 2191 cells/mm^2, death-to-preservation time of 10:45, preservation-to-surgery time of 220 hours, and negative bacterial and fungal rim cultures.

Epithelial defects were present in all eyes on the first postoperative day. There were 18 (2.0%) eyes in which the initial epithelial defect persisted for more than 14 days. There was no statistically significant correlation between donor age, death-to-preservation time, or preservation-to-surgery time and an increased risk of an initial PED. An initial PED occurred in 10 (5.7%) eyes with stromal scarring (including 9 with previous trachoma), 5 (1.1%) eyes with keratoconus, 2 (1.1%) eyes with corneal edema, and 1 (1.2%) eye with stromal dystrophy. The difference in initial PED between eyes with stromal scarring and those with other surgical indications was statistically significant ($P< 0.001$). The occurrence of an initial PED was not significantly associated with an increased risk of graft failure, a decreased likelihood of obtaining a final visual acuity of 20/40 or better, or an increased likelihood of a final visual outcome of 20/200 or worse.

Figure 10. Graft Survival Probability vs Donor Age



P-values: Cox proportional hazard regression/Wald chi-square test.

Donor age <45 years (n = 171; clear grafts under observation at 1, 3, and 5 years = 145, 101, and 83, respectively

Donor age 45-54 years (n =251; clear grafts under observation at 1, 3, and 5 years = 207, 141, and 78, respectively).

Donor age 55-59 years (n = 174; clear grafts under observation at 1, 3, and 5 years = 143, 96, and 64, respectively).

Donor age ≥60 (n = 314; clear grafts under observation at 1, 3, and 5 years = 207, 167, and 99, respectively).

Universal Risk Factors vs Graft Survival

The impact of universal risk factors is summarized in Table 5. Whereas multiple variables were found to be significantly associated with an increased risk of graft failure on univariate analysis, recipient graft size was the only variable that was also significant on multivariate analysis.

Table 5. Primary Optical Adult Penetrating Keratoplasty: Risk Factors vs Graft Survival Probability

Variable	HR[1] (95% CI)	*P* Value[1]	*P* Value[2]
Surgical variable			
Surgical diagnosis	25.21 (12.97, 49.01)	<0.001	<0.001
Patient age	1.24 (1.21, 1.31)	<0.001	0.259
Previous glaucoma surgery	9.44 (5.58, 15.97)	<0.001	0.521
Previous cataract surgery	4.97 (3.51, 7.03)	<0.001	0.073
Suture technique	2.06 (1.46, 2.90)	<0.001	0.377
Recipient graft size	0.84 (0.75, 0.93)	<0.001	0.020
Concomitant glaucoma surgery	5.41 (1.71, 17.12)	<0.001	0.380
Concomitant cataract surgery	3.74 (2.71, 5.16)	<0.001	0.152
Subsequent glaucoma surgery	2.56 (1.13, 5.79)	<0.001	0.691
Subsequent cataract surgery	1.07 (0.40, 2.89)	0.896	
Complications (any)	2.65 (1.92, 3.65)	<0.001	0.178

HR = hazard ratio; CI = confidence interval
[1] Univariate Cox proportional hazard regression/Wald chi-square test.
[2] Multivariate Cox proportional hazard regression/Wald chi-square test.

Surgical Variables

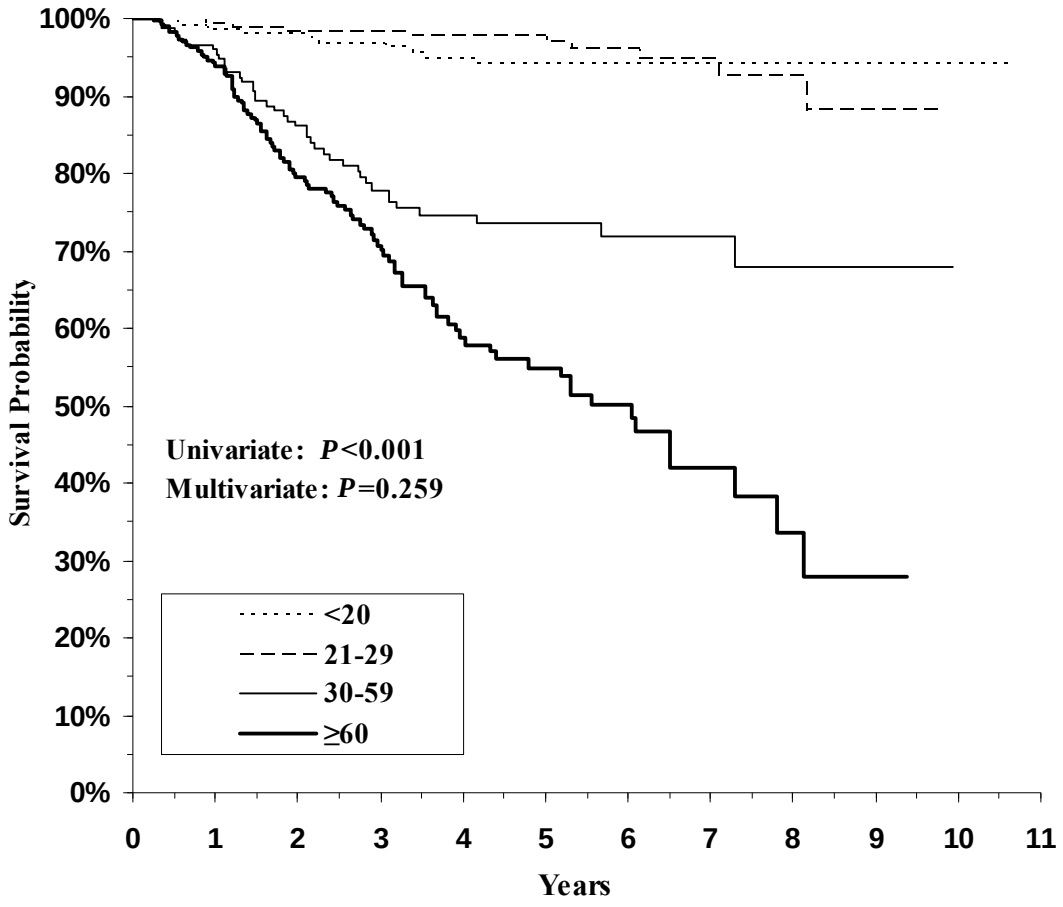
The most significant surgical variable affecting the probability of graft survival was the indication for which the procedure was performed. The statistical significance of surgical diagnosis as a risk factor for graft failure was present on univariate analysis (HR = 25.21; CI = 12.97, 49.01; $P< 0.001$) and multivariate analysis ($P<0.001$).Compared with keratoconus, a significantly increased risk of graft failure existed for PKP performed for corneal edema (HR = 21.83; 95% CI = 13.04, 36.45; $P<0.001$), stromal

scarring (HR = 8.72; 95% CI = 5.00, 15.22; $P<0.001$), and stromal dystrophy (HR = 3.94; 95% CI = 1.90, 8.18; $P<0.001$).

Patient age was directly associated with a significantly increased risk of graft failure on univariate, but not multivariate, analysis ($P<0.001$, $P = 0.259$). Among all cases, 5-year probability of graft survival was 94.0% for patients ≤20 years of age, 97.7% for those 21 to 29 years of age, 73.6% for those 30 to 59 years of age, and 54.5% for those 60 years of age or older (Figure 11). Within the surgical categories, increasing age was associated with a statistically insignificant increased risk of graft failure in eyes with keratoconus (HR = 1.05; 95% CI = 0.77, 1.42; $P = 0.747$), corneal edema (HR = 1.03; 95% CI = 0.93, 1.21; $P = 0.594$), stromal scarring (HR = 1.06; 95% CI = 0.93, 1.21; $P = 0.362$), and stromal dystrophy (HR = 1.11; 95% CI = 0.90, 1.36; $P = 0.324$).

Graft size was inversely associated with a significantly increased risk of graft failure on both univariate and multivariate analyses ($P<0.001$, $P = 0.02$, respectively). Five-year probability of graft survival was 88.4% for grafts that were ≥8.00 mm, 85.4% for those that were 7.50 mm to 7.75 mm, 76.2% for those that were 7.00 to 7.25 mm, and 58.1% for those that were <7.00 mm (Figure 12). The inverse association between graft size and an increased risk of graft failure was strongest for the surgical categories of keratoconus ($P = 0.02$) and stromal scarring ($P = 0.02$).

Figure 11. Graft Survival Probability vs Patient Age



P-values = Cox proportional hazard regression/Wald chi-square test.

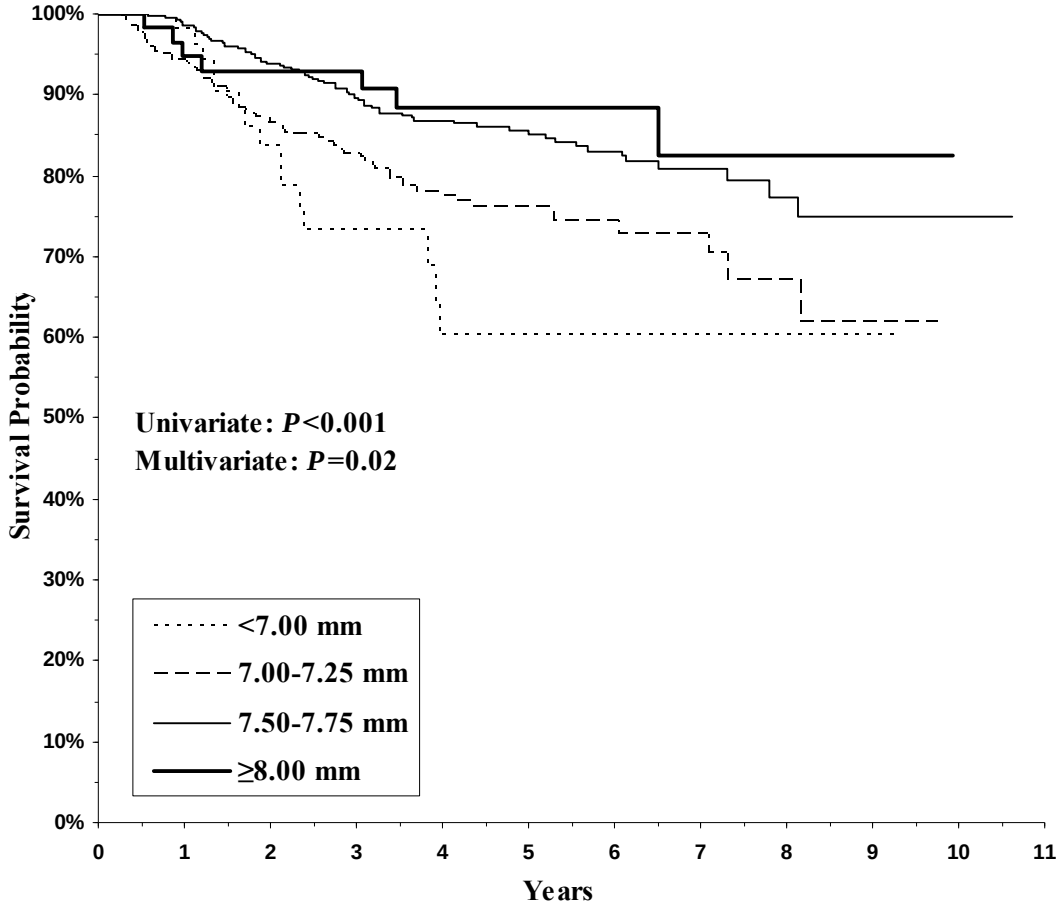
Patient age <20 years (n = 207; clear grafts under observation at 1, 3, and 5 years = 192, 148, and 89, respectively).

Patient age 21-29 years (n = 244; clear grafts under observation at 1, 3, and 5 years = 228, 175, and 121, respectively).

Patient age 30-59 years (n = 181; clear grafts under observation at 1, 3, and 5 years = 130, 93, and 75, respectively).

Patient age ≥ 60 years (n = 278; clear grafts under observation at 1, 3, and 5 years = 152, 89, and 39, respectively).

Figure 12. Graft Survival Probability vs Recipient Graft Size



P-values: Cox proportional hazard regression/Wald chi-square test.

Recipient graft size <7.00 mm (n = 58; clear grafts under observation at 1, 3, and 5 years = 37, 16, and 11, respectively).

Recipient graft size 7.00-7.25 mm (n = 331; clear grafts under observation at 1, 3, and 5 years = 238, 156, and 84, respectively).

Recipient graft size 7.50-7.75 mm (n = 463; clear grafts under observation at 1, 3, and 5 years = 378, 286, and 200, respectively).

Recipient graft size ≥8.00 mm (n = 58; clear grafts under observation at 1, 3, and 5 years = 49, 47, and 29, respectively).

Complications

The prevalence of postoperative complications after primary adult optical PKP is summarized in Table 6. One or more complications occurred in 362 (39.8%) eyes, ranging from a low of 22.9% in eyes with stromal dystrophy to a high of 54.9% in eyes with stromal scarring. The most common complication was endothelial rejection episodes (17.3%; range, 15.1%-21.3%), followed by glaucoma worsening (15.5%; range, 2.4%-30.3%), bacterial keratitis (5.8%; range, 2.4%-9.1%), late-onset PED (3.4%; range, 0%-5.9%), wound dehiscence (1.6%; range, 1.1%-2.7%), primary graft failure (0.1%), and endophthalmitis (0.1%).

There were statistically significant differences among the surgical indications with respect to the prevalence of the occurrence of one or more complications ($P<0.001$). In addition, statistically significant differences occurred in the prevalence of the specific complications of endothelial rejection episodes ($P = 0.01$), glaucoma worsening ($P<0.001$), bacterial keratitis ($P = 0.04$), and late-onset PED ($P = 0.02$) but not wound dehiscence, primary graft failure, or endophthalmitis.

The impact of the occurrence of one or more postoperative complications on the probability of graft survival is depicted in Figure 13. The 5-year probability of graft survival was 69.2% in eyes that experienced complications, compared with 88.8% in eyes in which complications did not occur. The occurrence of one or more complications was significantly associated with an increased risk of graft failure on univariate analysis (HR = 2.65; 95% CI = 1.92, 3.65; $P<0.001$) but not on multivariate analysis (HR = 0.427; 95% CI = 0.123, 1.473; $P = 0.178$).

The lack of statistical significance on multivariate analysis appeared to be attributable to the paramount importance of surgical indication category as the most important factor related to whether or not a graft was at increased risk of failure. In eyes with corneal edema, complications were significantly associated with an increased risk of graft failure on both univariate (HR = 2.65; 95% CI = 1.60, 4.38; $P<0.001$) and multivariate analyses

(HR = 5.83; 95% CI = 1.53, 22.27; P<0.001), with a reduction in 5-year survival probability from 71.1% to 23.0% (Figure 14). In eyes with stromal dystrophy, complications were associated with a 2-fold increased risk of graft failure on univariate analysis that was not statistically significant (HR = 1.99; 95% CI = 0.60, 6.61; P = 0.240), with a reduction in 5-year survival probability from 89.1% to 74.8% (Figure 15). In eyes with stromal scarring, complications were associated with only a slightly increased risk of graft failure on univariate analysis that was not statistically significant (HR = 1.09; 95% CI = 0.58, 2.05; P = 0.772) and with a marginal reduction in 5-year survival probability from 72.3% to 70.2% (Figure 16). Keratoconus was not associated with an increased risk of graft failure after development of postoperative complications (HR = 0.44; 95% CI = 0.13, 1.52; P = 0.179), with 5-year graft survival that was actually increased from 94.5% to 97.5% in eyes that experienced complications (Figure 17). The risk of complication-related graft failure varied significantly among the groups (P = 0.02).

The impact of specific complications on the probability of graft survival is summarized in Table 7. Among all cases, the following complications were associated with an increased risk of graft failure on univariate analysis: endothelial rejection episodes (HR = 2.36; P<0.001) (Figure 18), glaucoma worsening (HR = 2.58; P<0.001) (Figure 19), bacterial keratitis (HR = 2.42; P = 0.048) (Figure 20), and PEDs (HR =2.42; P = 0.016) (Figure 21). Specific complications were not associated with a significantly increased risk of graft failure on multivariate analysis because of the strong association between surgical indications and the risk of specific complication-associated graft failure.

Endothelial rejection episodes were associated with graft failure in 33 (82.5%) eyes with corneal edema, 11 (32.4%) eyes with stromal scarring, and 4 (30.8%) eyes with stromal dystrophy. Endothelial rejection episodes were not associated, however, with a single case of graft failure in 70 eyes with keratoconus that had at least 1 rejection episode. They were associated with an HR that was >1.0 for in eyes with stromal dystrophy (HR = 3.89), corneal edema (HR = 2.49), and stromal scarring (HR = 1.43). Statistical

significance on univariate analysis was demonstrated only for eyes with corneal edema (P<0.001) (Figure 22) and stromal dystrophy (P = 0.023) (Figure 23).

Bacterial keratitis was associated with an HR that was >1.0 in eyes with stromal scarring (HR = 1.63), keratoconus (HR = 1.26), and corneal edema (HR = 1.18), although this increased risk was not statistically significant. Bacterial keratitis was not associated with graft failure in the 2 eyes with stromal dystrophy in which it occurred. In addition, PEDs were associated with an HR that was >1.0 in eyes with stromal scarring (HR = 2.31) and corneal edema (1.08), although this increased risk was not statistically significant. Glaucoma escalation was associated only with an HR that was >1.0 in eyes with corneal edema (HR = 1.39), although this increased risk was not statistically significant.

Table 6. Primary Adult Optical Penetrating Keratoplasty: Postoperative Complications vs Surgical Indication

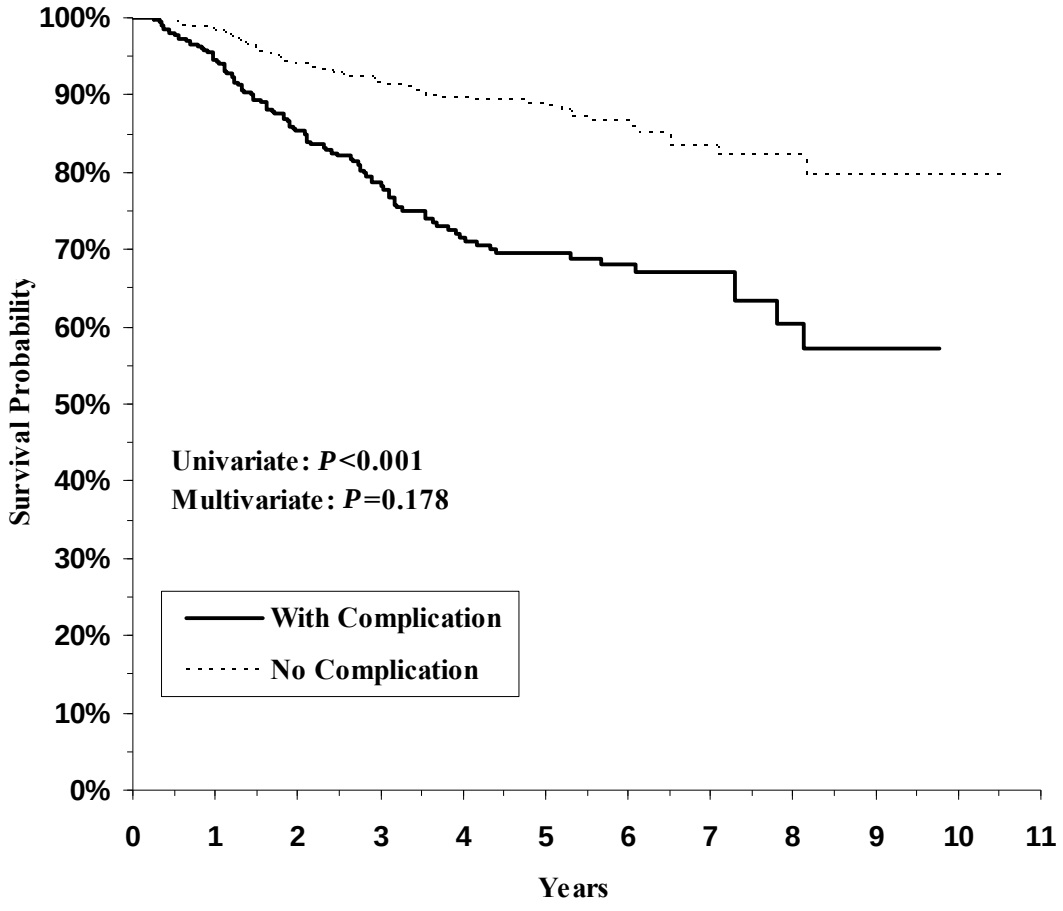
	All	Keratoconus	Corneal Edema	Stromal Scarring	Stromal Dystrophy	*P* Value[1]
Eyes, n	910	464	188	175	83	
Age, y						
Mean	40.1	22.7	65.5	61.8	34.2	<0.001
Range	12-95	12-78	29-65	16-92	19-77	
Preexisting glaucoma, n (%)						
Medical Rx only	32 (3.5)	0	23 (12.2)	9 (5.1)	0	<0.001
Medical + surgical Rx	34 (3.7)	0	28 (14.9)	6 (3.4)	0	<0.001
All	66 (7.3)	0	51 (27.1)	15 (8.6)	0	<0.001
Pseudophakia/aphakia, n (%)						
Prior to PKP	172 (18.9)	3 (0.6)	155 (82.4)	14 (8.0)	0	<0.001
Concomitant with PKP	168 (18.5)	1 (0.2)	30 (15.6)	134 (76.6)	3 (3.6)	<0.001
All	340 (37.4)	4 (0.9)	185 (98.4)	148 (84.6)	3 (3.6)	<0.001
Complications, n (%)						
≥1 complication[2]	362 (39.8)	144 (31.0)	103 (54.8)	96 (54.9)	19 (22.9)	<0.001
Endothelial rejection episodes	157 (17.3)	70 (15.1)	40 (21.3)	34 (19.4)	13 (15.7)	0.01
Glaucoma worsening	141 (15.5)	35 (7.5)	57 (30.3)	47 (26.9)	2 (2.4)	<0.001
Bacterial keratitis	53 (5.8)	23 (5.0)	12 (6.4)	16 (9.1)	2 (2.4)	0.04
Persistent epithelial defect	31 (3.4)	12 (2.6)	11 (5.9)	8 (4.6)	0	0.02
Wound dehiscence	15 (1.6)	8 (1.7)	3 (1.6)	2 (1.1)	2 (2.4)	NS
Primary graft failure	1 (0.1)	0	0	0	1 (1.2)	NS
Endophthalmitis	1 (0.1)	0	0	1 (0.6)	0	NS

PKP = penetrating keratoplasty; NS = not significant.

[1]Wilcoxon log-rank sum test for age; chi-square for other variables.

[2]Some eyes had >1 complication.

Figure 13. Graft Survival Probability vs One or More Postoperative Complications: All Cases

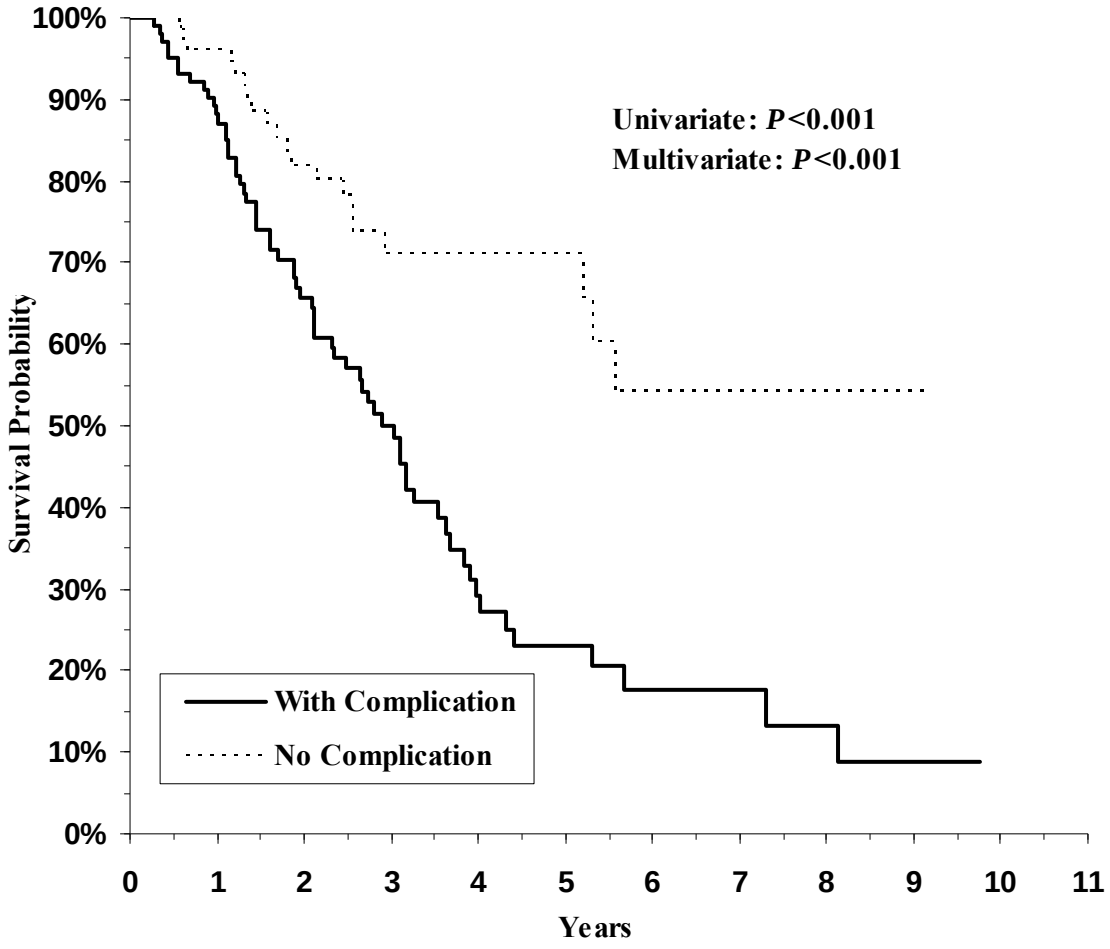


P-value: Cox proportional hazard regression/Wald chi-square test.

One or more complications (n = 362; clear grafts under observation at 1, 3, and 5 years = 249, 169, and 106, respectively).

No complications (n = 548; clear grafts under observation at 1, 3, and 5 years = 453, 336, and 218, respectively.

Figure 14. Graft Survival Probability vs One or More Postoperative Complications: Corneal Edema

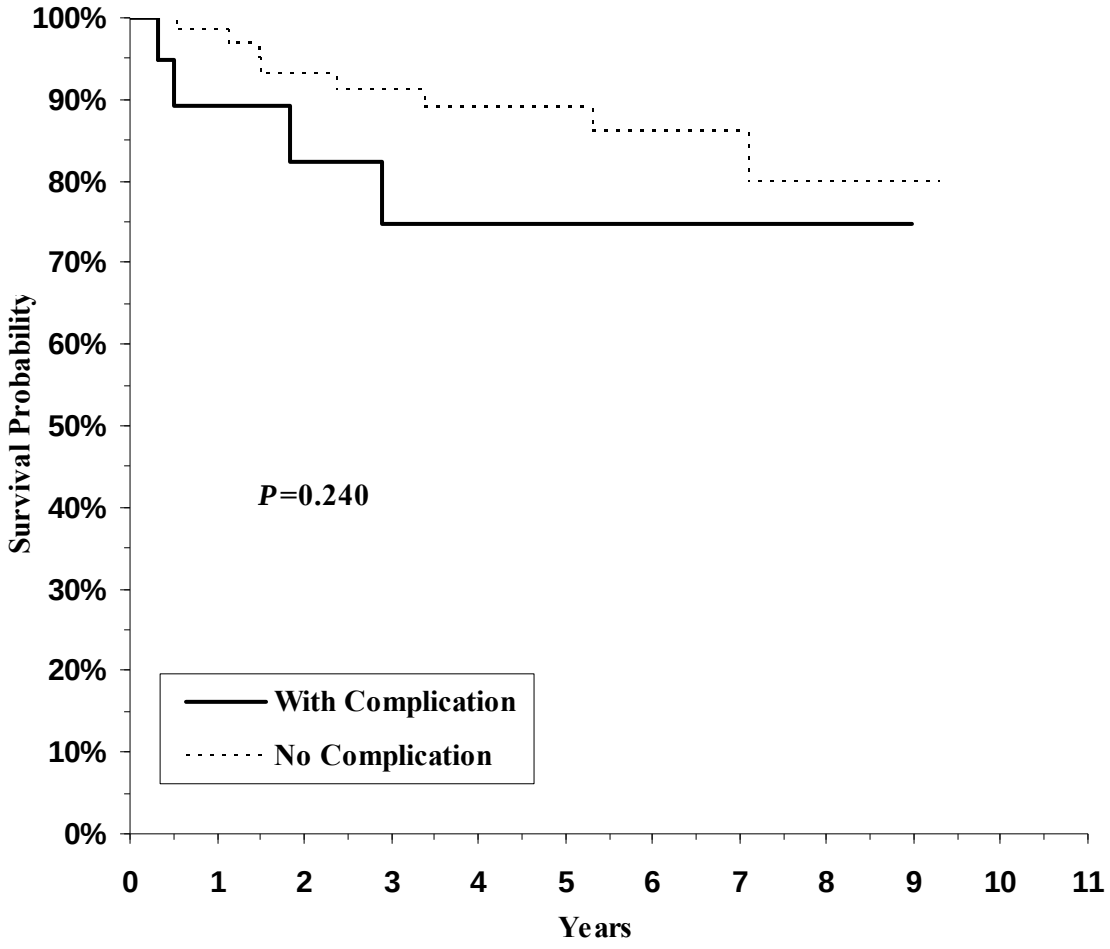


P-values: Cox proportional hazard regression/Wald chi-square test.

One or more complications (n = 103; clear grafts under observation at 1, 3, and 5 years = 35, 15, and 6, respectively).

No complications (n = 85; clear grafts under observation at 1, 3, and 5 years = 51, 25, and 11, respectively).

Figure 15. Graft Survival Probability vs One or More Postoperative Complications: Stromal Dystrophy

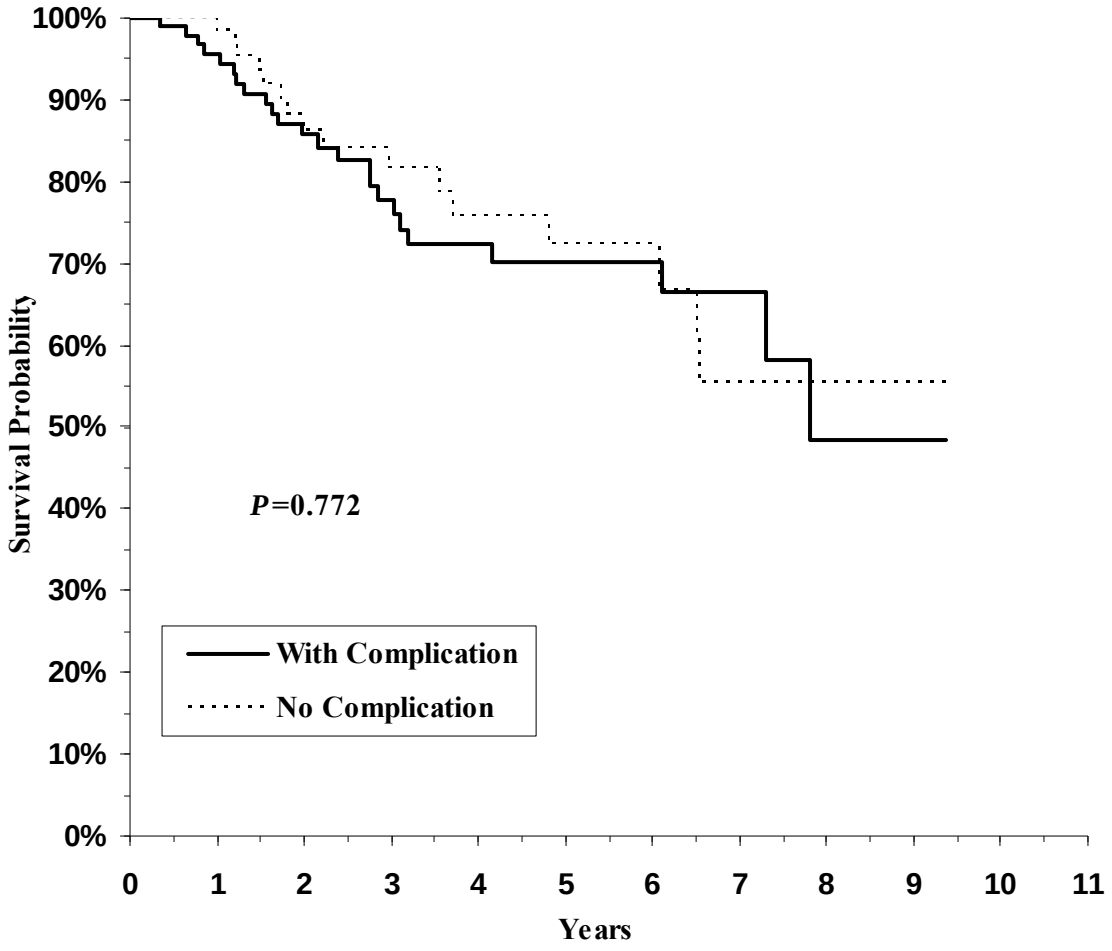


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

One or more complications (n = 19; clear grafts under observation at 1, 3, and 5 years = 14, 10, and 8, respectively).

No complications (n = 64; clear grafts under observation at 1, 3, and 5 years = 54, 39, and 29, respectively).

Figure 16. Graft Survival Probability vs One or More Postoperative Complications: Stromal Scarring

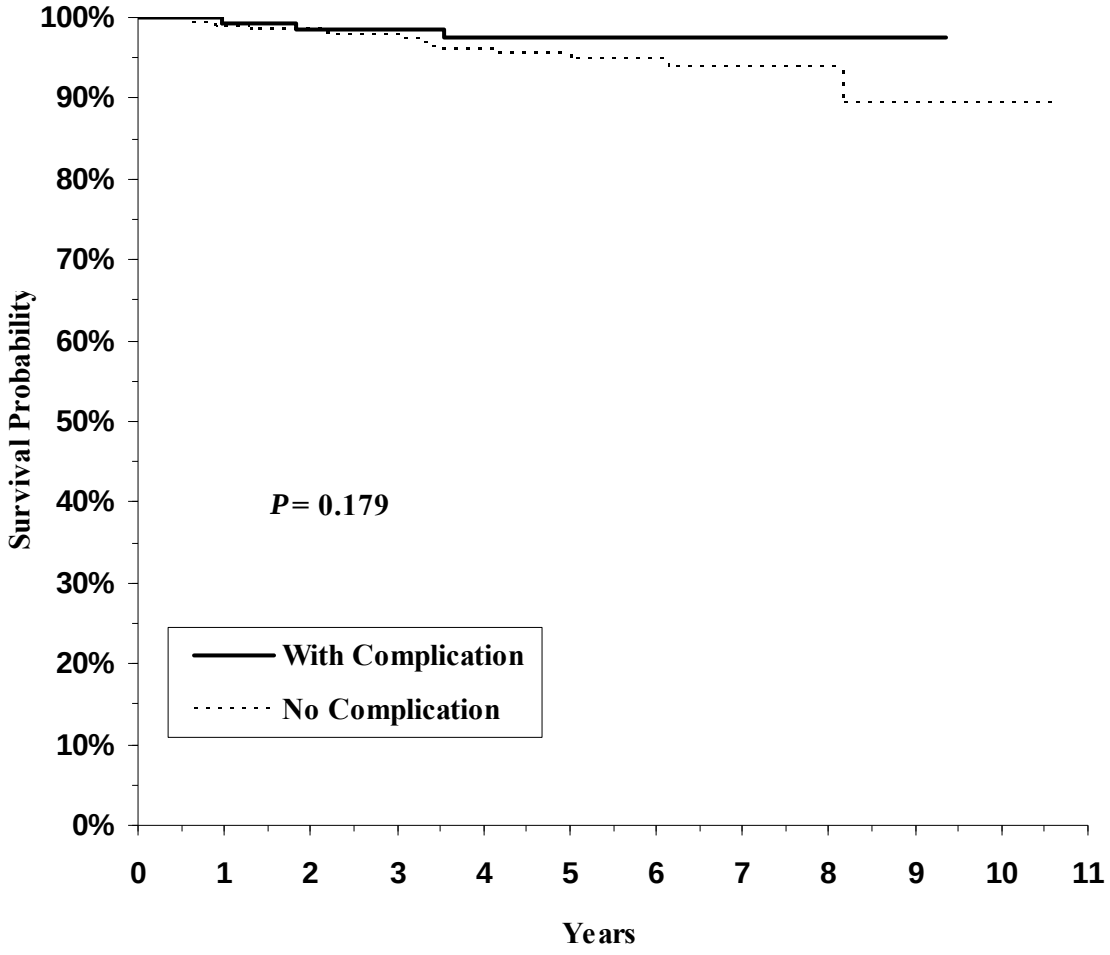


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

One or more complications (n = 96; clear grafts under observation at 1, 3, and 5 years = 62, 37, and 22, respectively).

No complications (n = 79; clear grafts under observation at 1, 3, and 5 years = 50, 25, and 14, respectively).

Figure 17. Graft Survival Probability vs One or More Postoperative Complications: Keratoconus



P-value: Cox univariate proportional hazard regression/Wald chi-square test.

One or more complications (n = 144; clear grafts under observation at 1, 3, and 5 years = 138, 109, and 70, respectively).

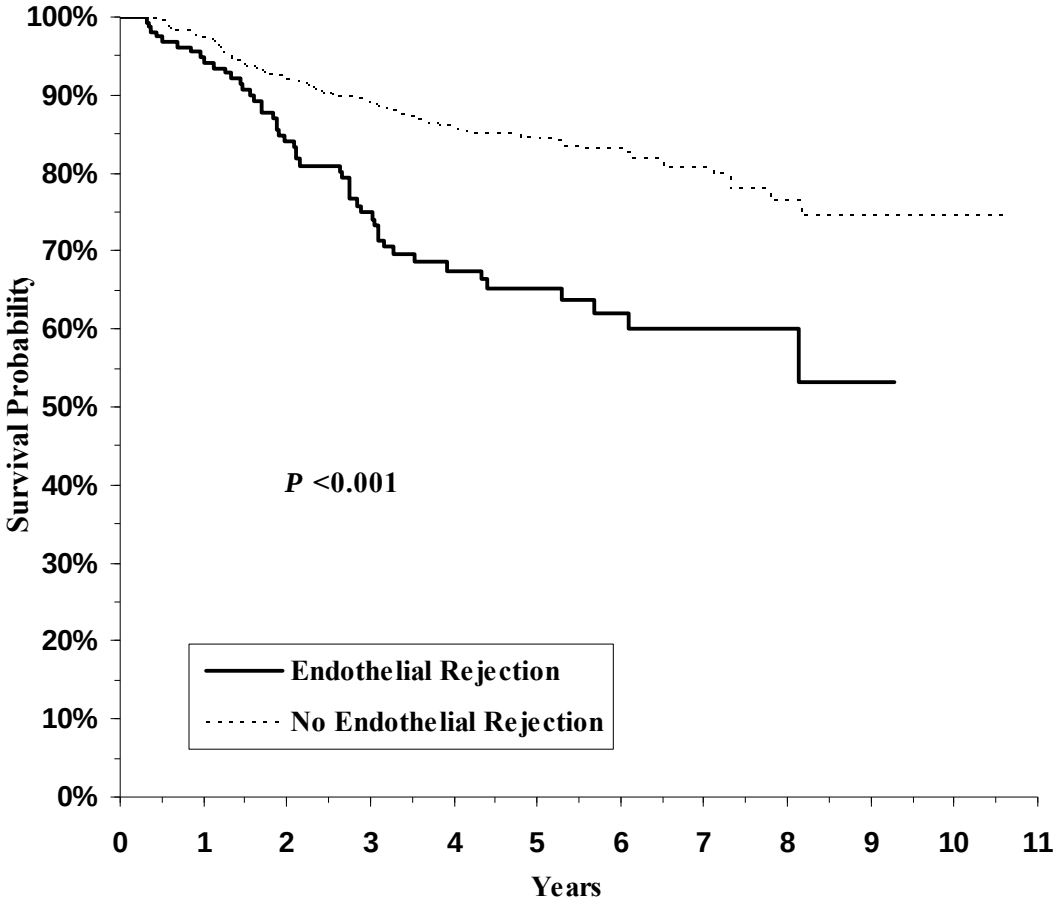
No complications (n = 320; clear grafts under observation at 1, 3, and 5 years = 298, 245, and 164, respectively).

Table 7. Postoperative Complications vs Graft Survival Probability vs Surgical Indication

	Without Complication			With Complication			Hazard Ratio[1] (95% Confidence Interval)	*P* Value[2]
	Graft Survival Probability,%			Graft Survival Probability, %				
	1 year	3 years	5 years	1 year	3 years	5 years		
Endothelial rejection episodes								
All	97.3	88.7	88.4	94.9	74.5	64.7	2.36 (1.68, 3.31)	<0.001
Keratoconus	98.7	97.6	95.4	100.0	100.0	100.0	†	†
Corneal edema	93.5	64.6	52.0	85.0	41.1	14.7	2.49 (1.60, 3.87)	<0.001
Stromal scarring	96.0	82.4	74.4	94.9	74.5	64.7	1.43 (0.72, 2.87)	0.310
Stromal dystrophy	98.6	91.9	90.0	84.6	61.7	61.7	3.89 (1.17, 12.92)	0.027
Glaucoma worsening								
All	97.5	88.1	84.4	93.4	75.8	62.2	2.58 (1.83, 3.64)	<0.001
Keratoconus	99.1	98.0	96.0	97.1	97.1	97.1	0.66 (0.09, 4.98)	0.689
Corneal edema	91.7	60.1	52.2	91.0	55.4	23.8	1.39 (0.90, 2.15)	0.142
Stromal scarring	98.2	78.4	68.0	93.2	82.1	78.6	0.93 (0.47, 1.87)	0.849
Stromal dystrophy	96.3	87.4	85.7	100.0	100.0	100.0	†	†
Bacterial keratitis								
All	96.9	86.8	81.8	96.3	79.4	67.1	1.74 (1.02.2.96)	0.048
Keratoconus	98.8	98.1	96.1	100.0	95.4	95.4	1.26 (0.17, 9.48)	0.822
Corneal edema	91.6	59.0	41.6	91.7	52.5	26.2	1.18 (0.54, 2.57)	0.623
Stromal scarring	97.2	80.5	72.6	93.8	69.4	57.8	1.63 (0.68, 3.88)	0.271
Stromal dystrophy	96.3	87.4	85.7	100.0	100.0	100.0	†	†
Persistent epithelial defect								
All	97.1	86.9	81.9	89.3	69.6	61.0	2.42 (1.33, 4.39)	0.016
Keratoconus	98.9	98.1	96.2	100.0	90.0	90.0	0.39 (0.04, 3.48)	0.401
Corneal edema	92.2	58.3	40.8	81.8	68.2	34.1	1.08 (0.47, 2.47)	0.863
Stromal scarring	97.8	81.0	72.5	72.9	58.3	58.3	2.31 (0.71, 7.55)	0.166
Stromal dystrophy	96.4	87.6	85.9	‡	‡	‡	‡	‡
Wound dehiscence								
All	96.7	86.0	80.6	100.0	77.4	77.4	1.15 (0.36, 3.60)	0.82

[1]Univariate Cox proportional hazard regression (†not performed because no graft failures were associated with this complication; ‡ not performed because this complication did not occur after penetrating keratoplasty for this surgical indication). [2] Wald chi-square test

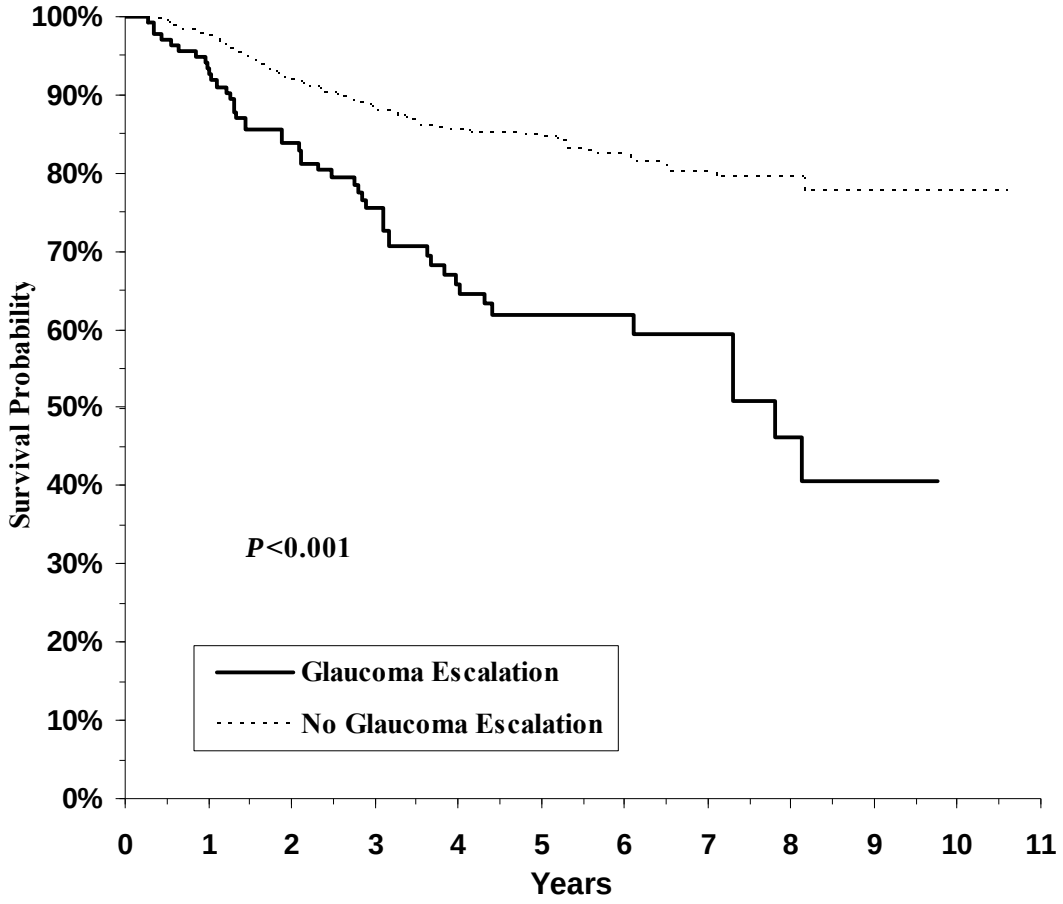
Figure 18. Graft Survival Probability vs Endothelial Rejection Episodes: All Cases



P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Endothelial rejection episodes (n = 157; clear grafts under observation at 1, 3, and 5 years = 104, 70, and 44, respectively).
No endothelial rejection episodes (n = 753; clear grafts under observation at 1, 3, and 5 years = 598, 435, and 280, respectively).

Figure 19. Graft Survival Probability vs Glaucoma Worsening: All Cases

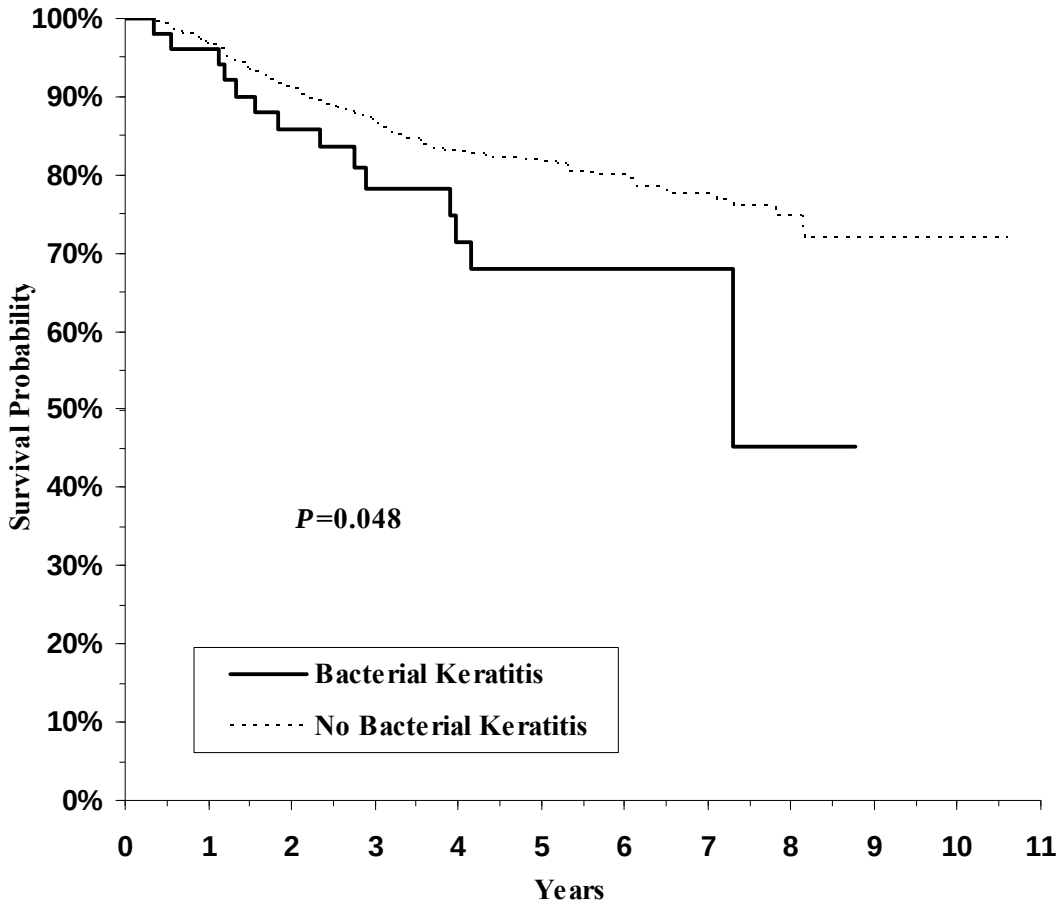


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Glaucoma worsening (n = 141; clear grafts under observation at 1, 3, and 5 years = 84, 59, and 30, respectively).

No glaucoma worsening (n = 769; clear grafts under observation at 1, 3, and 5 years = 618, 446, and 294, respectively).

Figure 20. Graft Survival Probability vs Bacterial Keratitis: All Cases

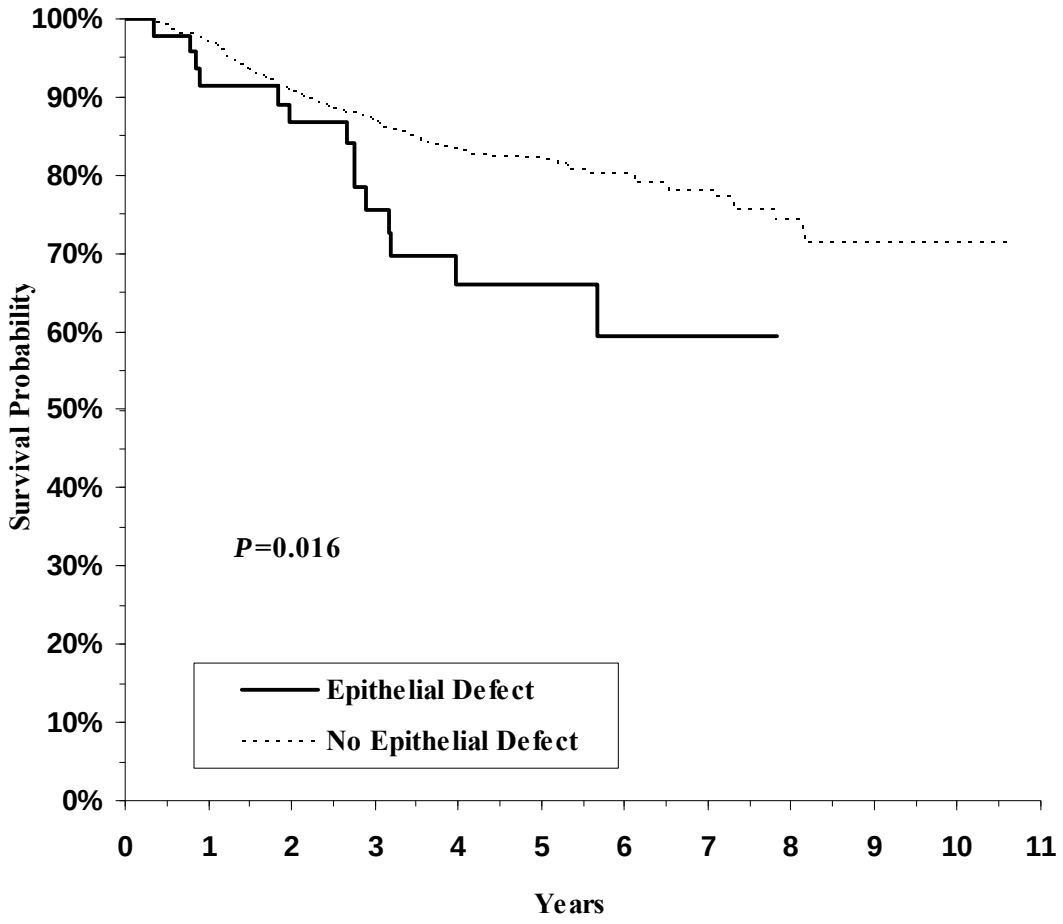


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Bacterial keratitis (n = 53; clear grafts under observation at 1, 3, and 5 years = 38, 26, and 16, respectively).

No bacterial keratitis (n = 857; clear grafts under observation at 1, 3, and 5 years = 664, 479, and 308, respectively).

Figure 21. Graft Survival Probability vs Persistent Epithelial Defect: All Cases

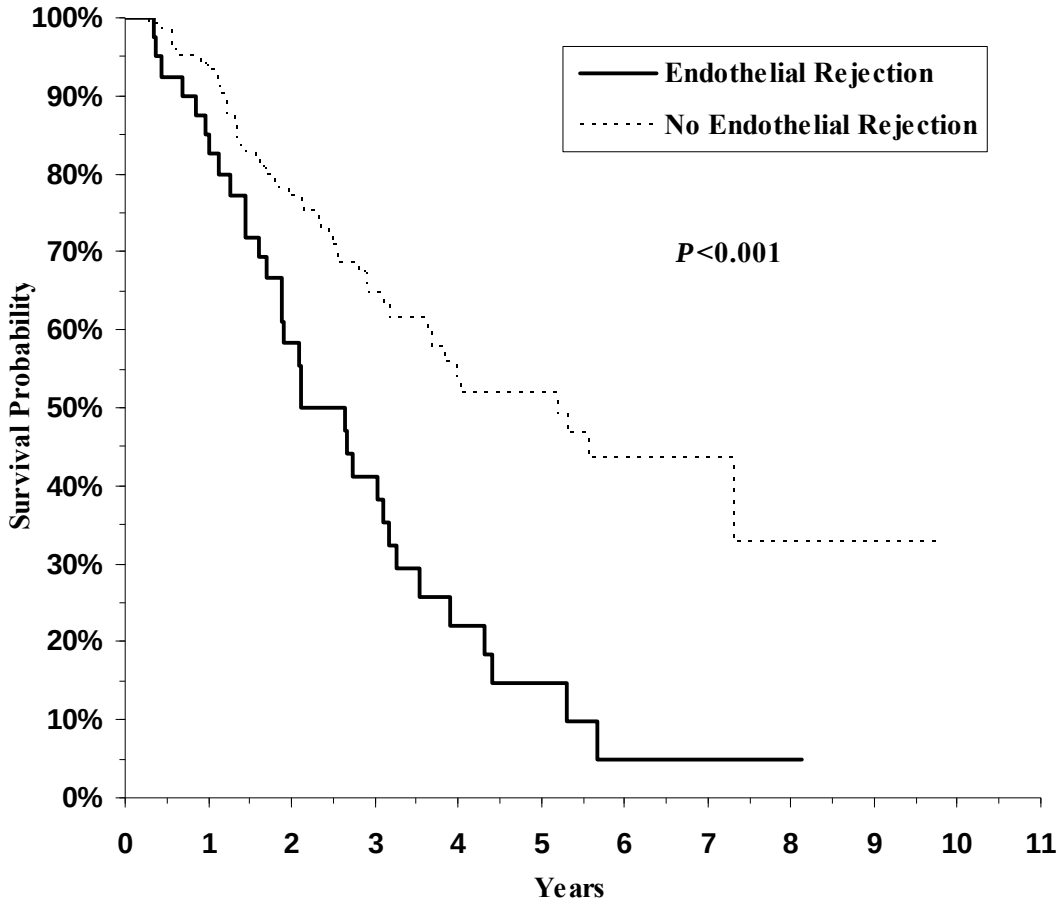


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Persistent epithelial defect (n = 31; clear grafts under observation at 1, 3, and 5 years = 20, 15, and 8, respectively).

No persistent epithelial defect (n = 879; clear grafts under observation at 1, 3, and 5 years = 682, 490, and 316, respectively).

Figure 22. Graft Survival Probability vs Endothelial Rejection Episodes: Corneal Edema

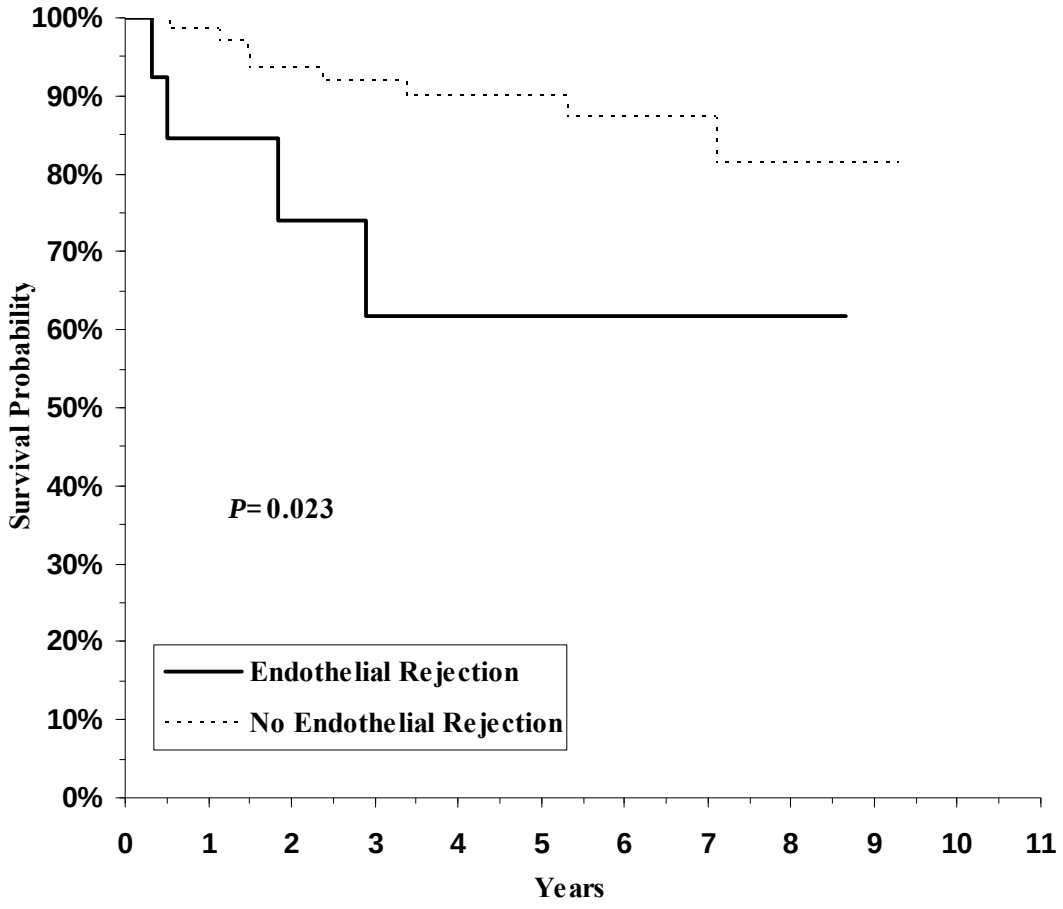


P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Endothelial rejection (n = 40; clear grafts under observation at 1, 3, and 5 years = 7, 3, and 0, respectively).

No endothelial rejection (n = 148; clear grafts under observation at 1, 3, and 5 years = 86, 40, and 17, respectively).

Figure 23. Graft Survival Probability vs Endothelial Rejection Episodes: Stromal Dystrophy



P-value: Cox univariate proportional hazard regression/Wald chi-square test.

Endothelial rejection (n = 13; clear grafts under observation at 1, 3, and 5 years = 9, 5, and 4, respectively).

No endothelial rejection (n = 70; clear grafts under observation at 1, 3, and 5 years = 56, 49, and 33, respectively).

Visual Acuity

Preoperatively, a BCVA of 20/40 or better was present in only 6 (0.7%) eyes, whereas 747 (82.1%) eyes were suffering from vision that was 20/200 or worse. Postoperatively, the final BCVA had improved to 20/40 or better in 409 (44.9%) eyes, whereas only 237 (26.0 %) remained 20/200 or worse ($P<0.001$) (Table 8, Figure 24). Among grafts that remained clear, a BCVA of 20/40 or better was present in 409 (54.0%) eyes, whereas vision of 20/200 or worse was present in only 105 (13.9%) eyes (Table 9, Figure 25). Overall, improvement in vision occurred in 750 (82.4%) eyes, remained the same in 97 (10.7%) eyes, and worsened in 63 (6.9%) eyes.

There were significant differences in the final BCVA among the surgical categories, with the best visual prognosis in eyes with keratoconus and stromal dystrophy ($P<0.001$). Among all grafts, a BCVA of 20/40 or better was achieved in 336 (72.4 %) eyes with keratoconus and in 53 (63.9%) eyes with stromal dystrophy but in only 11 (6.3%) eyes with stromal scarring and in 9 (4.8%) eyes with corneal edema. Conversely, only 14 (3.0%) eyes with keratoconus and 6 (7.2%) eyes with stromal dystrophy had a BCVA of 20/200 or worse, in contrast to 131 (69.7%) eyes with corneal edema and 84 (48.0%) eyes with stromal scarring.

Among grafts that remained clear, statistically significant differences in the final BCVA were still present among the surgical categories ($P<0.001$). A BCVA of 20/40 or better was obtained in 336 (75.3%) eyes with keratoconus and 53 (74.6%) eyes with stromal dystrophy but in only 9 (8.6%) eyes with corneal edema and in 11 (8.1%) eyes with stromal scarring. Conversely, only 5 (1.1%) eyes with keratoconus and no eyes with stromal dystrophy had a BCVA of 20/200 or worse, in contrast to 51 (48.6%) eyes with corneal edema and 49 (36.3%) eyes with stromal scarring.

In eyes with keratoconus, there were no significant differences in the final BCVA in eyes with or without VKC for all grafts (Table 10, Figure 26) or for those with clear grafts (Table 11, Figure 27).

Among all grafts with corneal edema (Table 12, Figure 28), a lower percentage of eyes with phakic corneal edema had a final BCVA that was 20/200 or worse, although these differences were not statistically significant ($P = 0.06$). However, among grafts that remained clear (Table 13, Figure 29), this difference became statistically significant ($P = 0.007$).

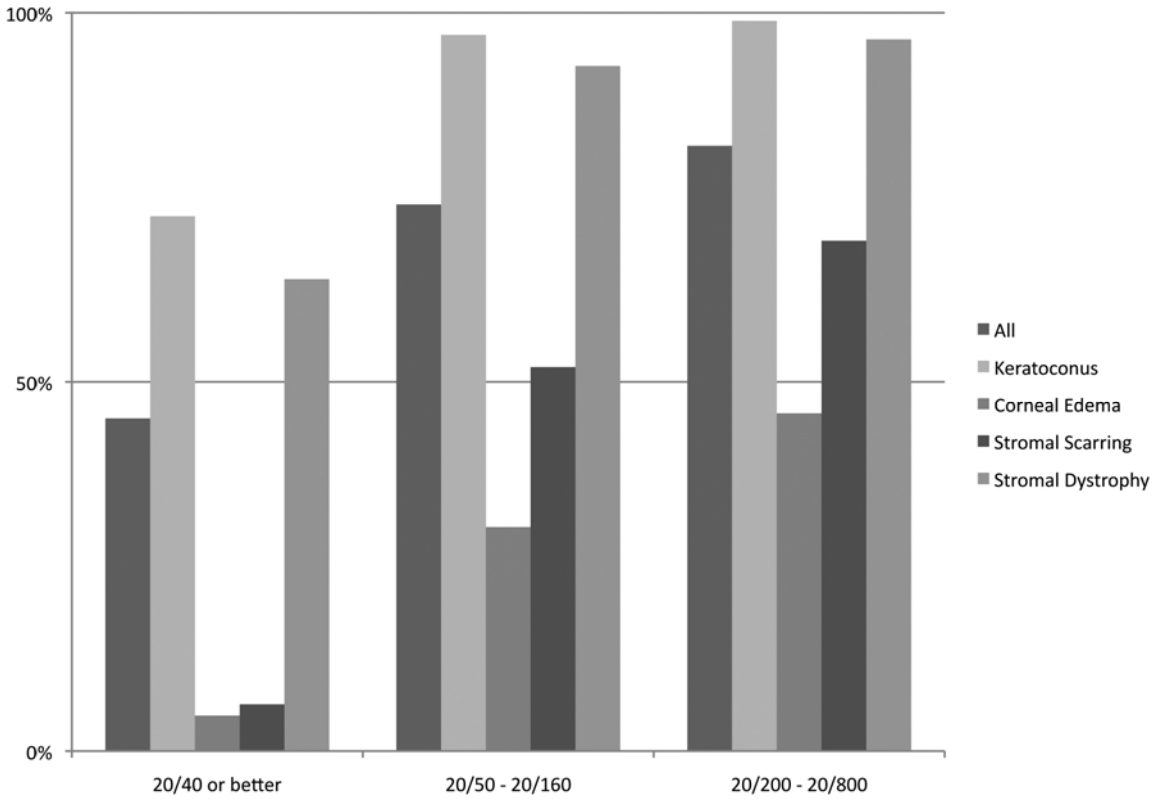
Among all grafts with stromal scarring (Table 14, Figure 30), a significantly higher percentage of eyes with scarring that was attributed to other (and, presumably, mostly herpetic) etiologies had a final BCVA that was 20/200 or worse than scarring that was attributed to trachoma, microbial keratitis, or trauma ($P = 0.02$). However, among grafts that remained clear (Table 15, Figure 31), this difference became statistically insignificant ($P = 0.58$).

Table 8. Primary Adult Optical Penetrating Keratoplasty: Final Best Corrected Visual Acuity (all grafts)

	All		Keratoconus		Corneal Edema		Stromal Scarring		Stromal Dystrophy	
Visual Acuity	n	Cum %	n	Cum %	n	Cum %	n	Cum %	n	Cum %
20/40 or better	409	45.0	336	72.4	9	4.8	11	6.3	53	63.9
20/50 to 20/160	264	74.0	114	97.0	48	30.3	80	52.0	24	92.8
20/200 to 20/800	73	82.0	9	98.9	29	45.7	30	69.1	3	96.4
CF	86	91.4	5	100.0	54	74.5	26	84.0	1	97.6
HM	53	97.3	0	100.0	33	92.0	20	95.4	0	97.6
LP	17	99.1	0	100.0	12	98.4	4	97.7	1	98.8
NLP	8	100.0	0	100.0	3	100.0	4	100.0	1	100.0
Total	910		464		188		175		83	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 24. Final Best Corrected Visual Acuity (all grafts)



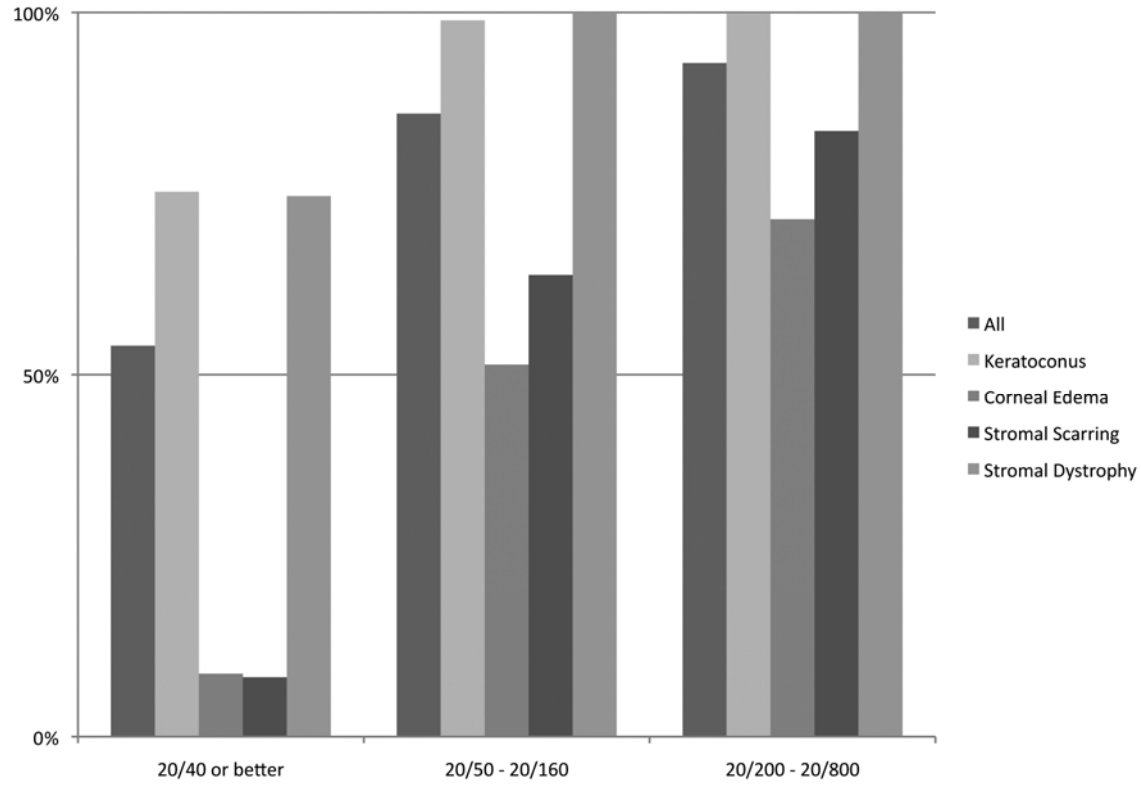
The differences among the surgical indication groups are statistically significant ($P< 0.001$).

Table 9. Primary Adult Optical Penetrating Keratoplasty: Final Best Corrected Visual Acuity (clear grafts only)

	All		Keratoconus		Corneal Edema		Stromal Scarring		Stromal Dystrophy	
Visual Acuity	n	Cum %	n	Cum %	n	Cum %	n	Cum %	n	Cum %
20/40 or better	409	54.0	336	75.3	9	8.6	11	8.1	53	74.6
20/50 to 20/160	243	86.1	105	98.9	45	51.4	75	63.7	18	100.0
20/200 to 20/800	52	93.0	4	99.8	21	71.4	27	83.7	0	100.0
CF	31	97.1	1	100.0	18	88.6	12	92.6	0	100.0
HM	16	99.2	0	100.0	9	97.1	7	97.8	0	100.0
LP	5	99.9	0	100.0	3	100.0	2	99.3	0	100.0
NLP	1	100.0	0	100.0	0	100.0	1	100.0	0	100.0
Total	757		446		105		135		71	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 25. Final Best Corrected Visual Acuity (clear grafts only)



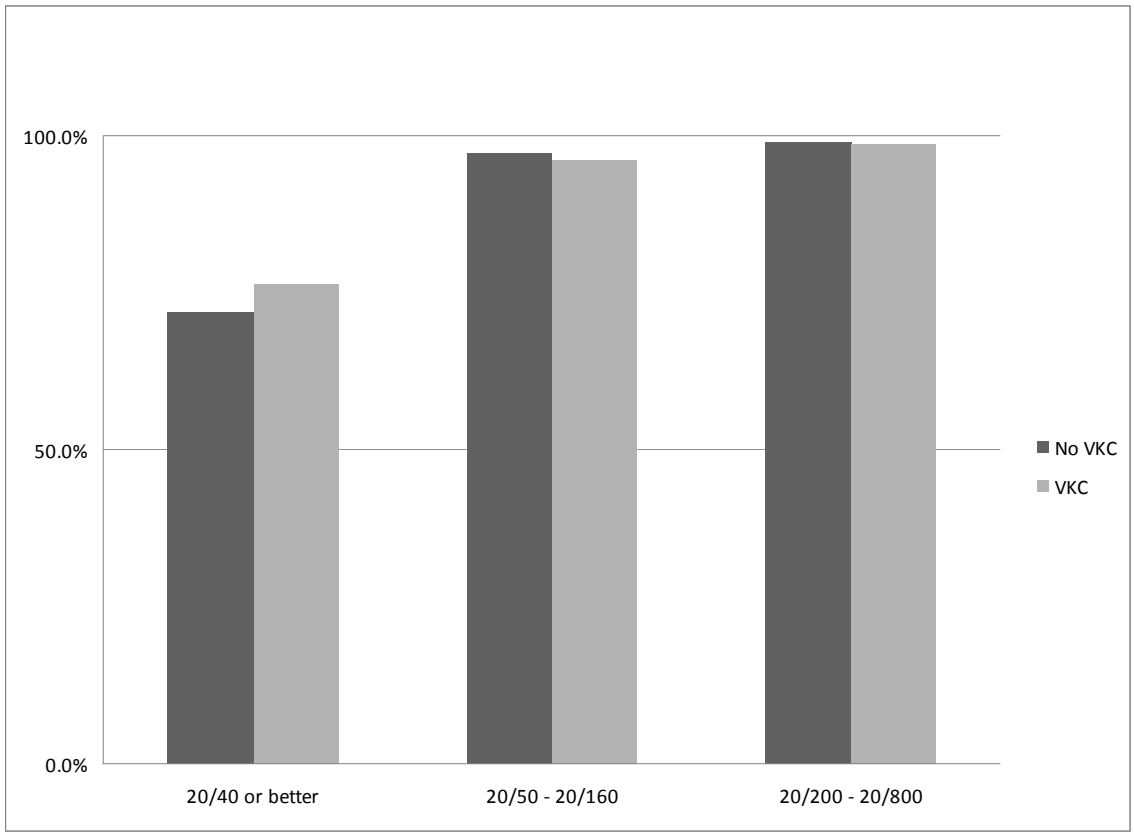
The differences among the surgical indication groups are statistically significant ($P<0.001$).

Table 10. Penetrating Keratoplasty for Keratoconus: Final Best Corrected Visual Acuity vs Presence or Absence of Vernal Keratoconjunctivitis (VKC) (all grafts)

	No VKC		VKC	
Visual Acuity	**n**	**Cum %**	**n**	**Cum %**
20/40 or better	276	71.9	61	76.2
20/50 to 20/160	97	97.1	16	96.3
20/200 to 20/800	7	98.9	2	98.8
CF	4	100.0	1	100.0
HM	0	100.0	0	100.0
LP	0	100.0	0	100.0
NLP	0	100.0	0	100.0
Total	384		80	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 26. Keratoconus: Final Best Corrected Visual Acuity (all grafts)



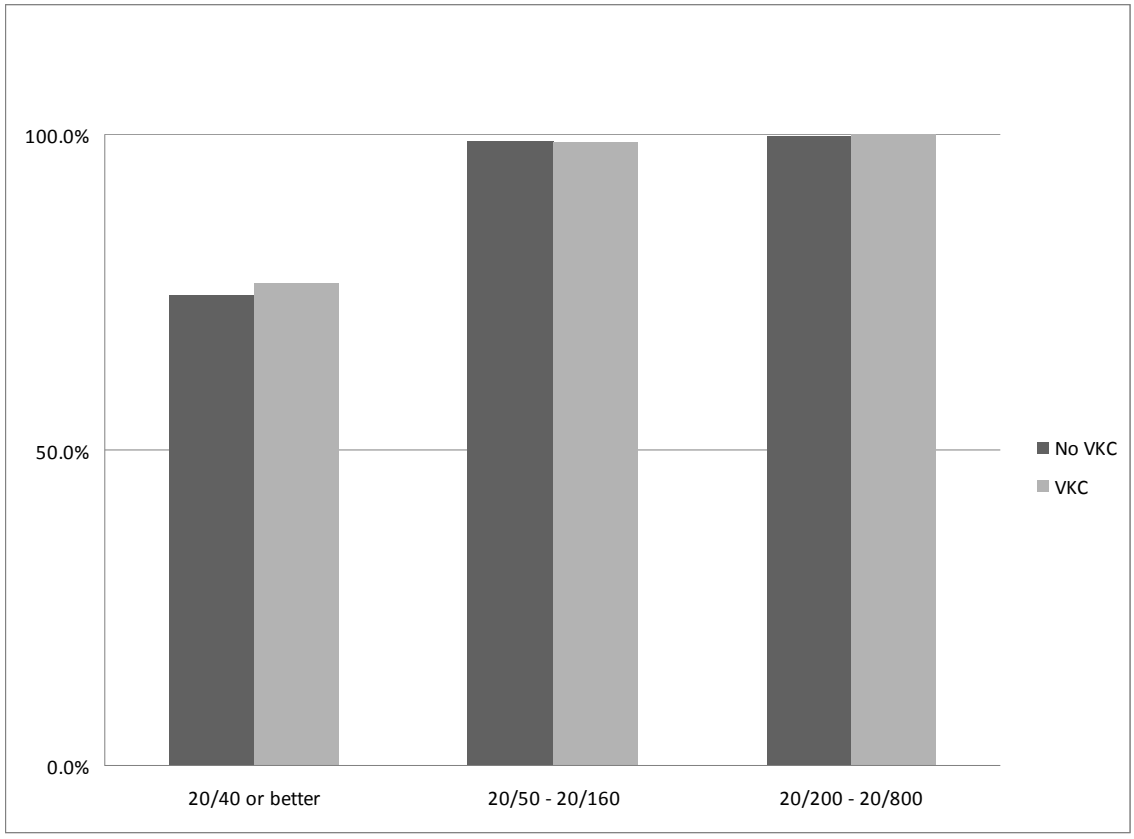
The difference between the surgical subgroups is not statistically significant.

Table 11. Penetrating Keratoplasty for Keratoconus: Final Best Corrected Visual Acuity vs Presence or Absence of Vernal Keratoconjunctivitis (VKC) (clear grafts only)

	No VKC		VKC	
Visual Acuity	**n**	**Cum %**	**n**	**Cum %**
20/40 or better	275	74.7	61	76.3
20/50 to 20/160	89	98.9	16	98.7
20/200 to 20/800	3	99.7	1	100.0
CF	1	100.0	0	100.0
HM	0	100.0	0	100.0
LP	0	100.0	0	100.0
NLP	0	100.0	0	100.0
Total	368		78	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 27. Keratoconus: Final Best Corrected Visual Acuity (clear grafts only)



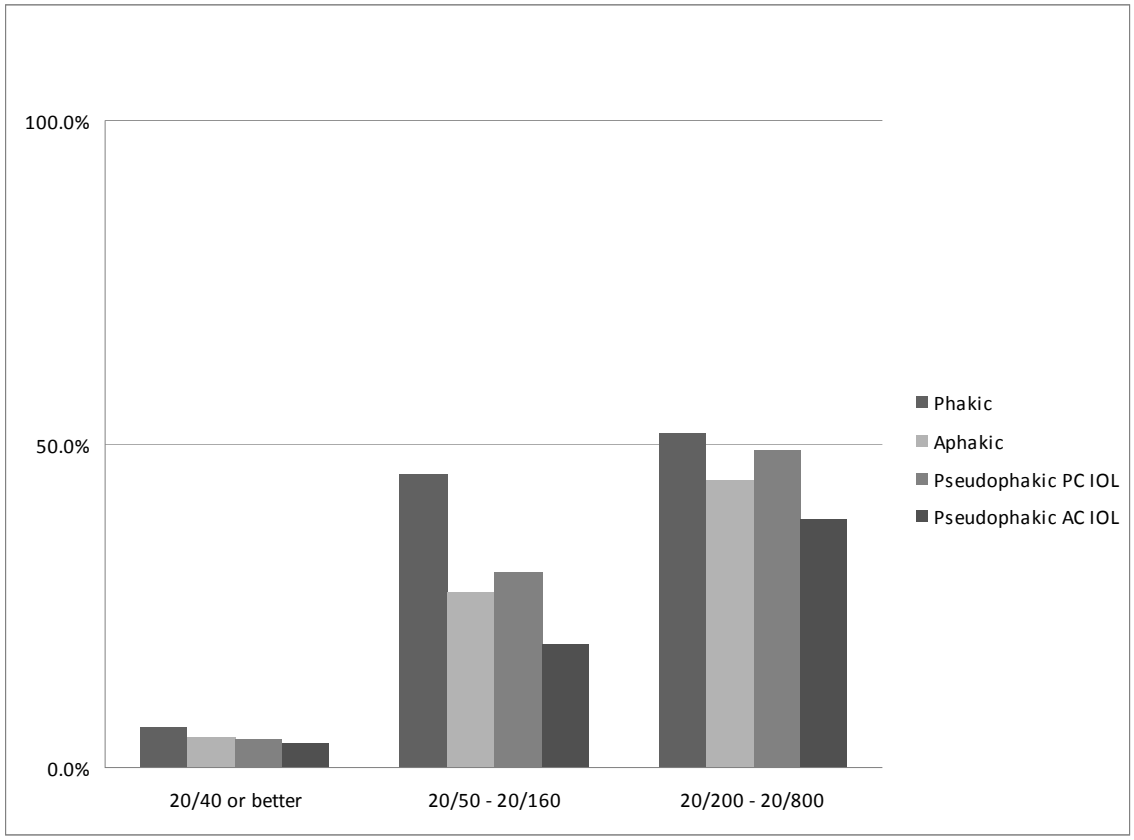
The difference between the surgical subgroups is not statistically significant.

Table 12. Penetrating Keratoplasty for Corneal Edema: Final Best Corrected Visual Acuity vs Lens Status (all grafts)

	Phakic		Aphakic		Pseudophakic PC IOL		Pseudophakic AC IOL	
Visual Acuity	**n**	**Cum %**	**n**	**Cum %**	**n**	**Cum %**	**n**	**Cum %**
20/40 or better	2	6.1	3	4.8	3	4.5	1	3.8
20/50 to 20/160	13	45.5	14	27.0	17	30.3	4	19.2
20/200 to 20/800	2	51.5	11	44.4	11	49.2	5	38.5
CF	11	84.8	19	74.6	17	72.7	7	65.4
HM	4	97.0	10	90.5	14	93.9	5	80.8
LP	0	97.0	4	96.8	4	100.0	4	100.0
NLP	1	100.0	2	100.0	0	100.0	0	100.0
Total	33		63		66		26	

PC IOL = posterior chamber intraocular lens; AC IOL = anterior chamber intraocular lens; Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 28. Corneal Edema: Final Best Corrected Visual Acuity (all grafts)



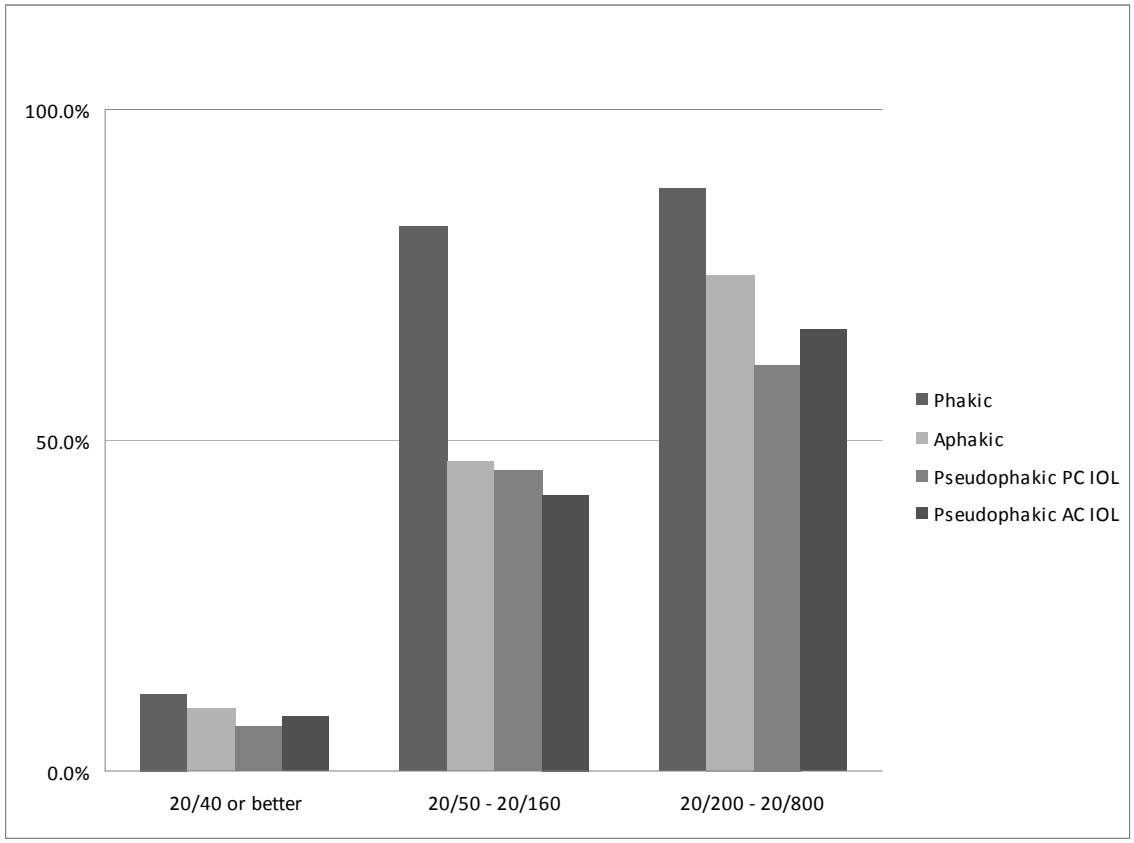
The difference between phakic and aphakic/pseudophakic eyes is not statistically significant (P = 0.06).

Table 13. Penetrating Keratoplasty for Corneal Edema: Final Best Corrected Visual Acuity vs Lens Status (clear grafts only)

	Phakic		Aphakic		Pseudophakic PC IOL		Pseudophakic AC IOL	
Visual Acuity	**n**	**Cum %**	**n**	**Cum %**	**n**	**Cum %**	**n**	**Cum %**
20/40 or better	2	11.7	3	9.4	3	6.8	1	8.3
20/50 to 20/160	12	82.4	12	46.9	17	45.5	4	41.7
20/200 to 20/800	1	88.2	9	75.0	7	61.4	4	66.7
CF	1	94.1	4	87.5	10	84.1	3	100.0
HM	1	100.0	3	96.9	5	95.5	0	100.0
LP	0	100.0	1	100.0	2	100.0	0	100.0
NLP	0	100.0	0	100.0	0	100.0	0	100.0
Total	17		32		44		12	

PC IOL = posterior chamber intraocular lens; AC IOL = anterior chamber intraocular lens; Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 29. Corneal Edema: Final Best Corrected Visual Acuity (clear grafts only)



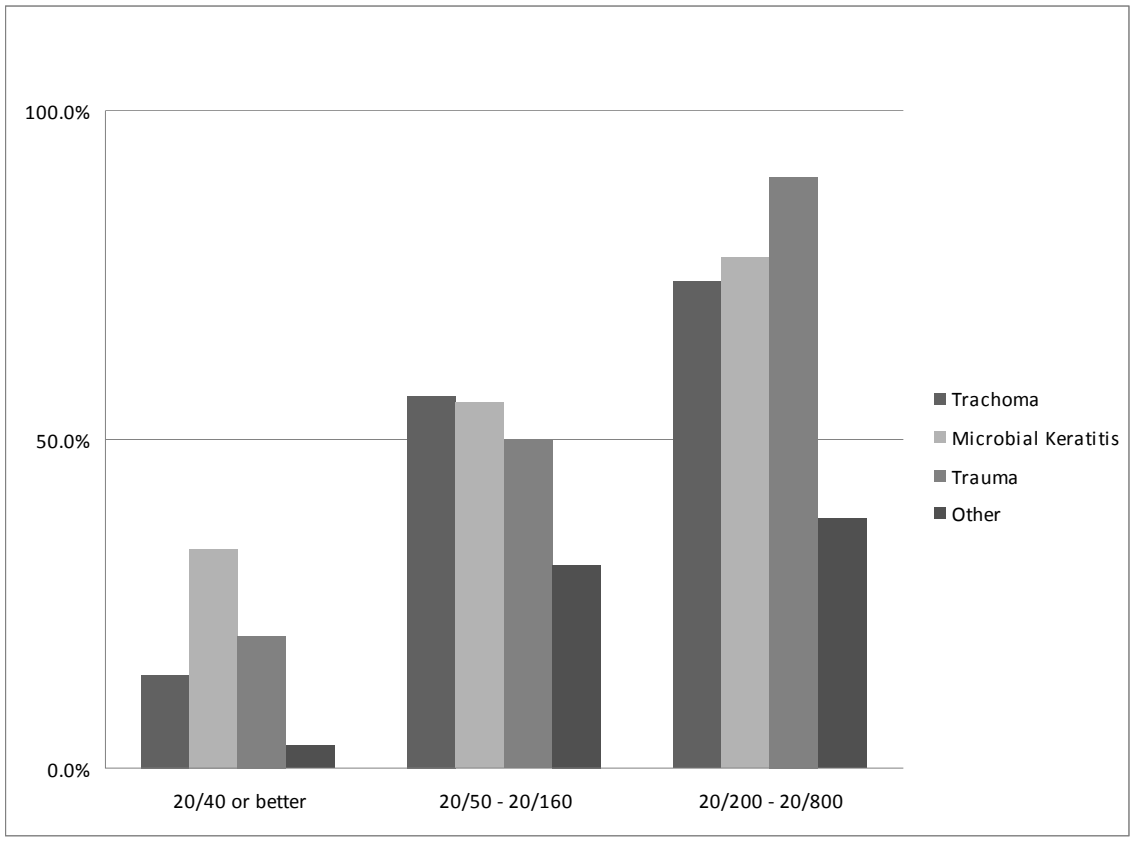
The difference between phakic and aphakic/pseudophakic eyes is statistically significant (P = 0.007).

Table 14. Penetrating Keratoplasty for Stromal Scarring: Final Best Corrected Visual Acuity vs Etiology (all grafts)

	Trachoma		Microbial Keratitis		Trauma		Other	
Visual Acuity	n	Cum %	n	Cum %	n	Cum %	n	Cum %
20/40 or better	5	14.2	3	33.3	2	20.0	1	3.4
20/50 to 20/160	67	56.7	2	55.6	3	50.0	8	31.0
20/200 to 20/800	22	74.0	2	77.8	4	90.0	2	37.9
CF	16	86.6	1	88.9	0	90.0	9	69.0
HM	12	96.1	0	88.9	1	100.0	7	93.1
LP	3	98.4	0	88.9	0	100.0	1	96.7
NLP	2	100.0	1	100.0	0	100.0	1	100.0
Total	127		9		10		29	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 30. Stromal Scarring: Final Best Corrected Visual Acuity (all grafts)



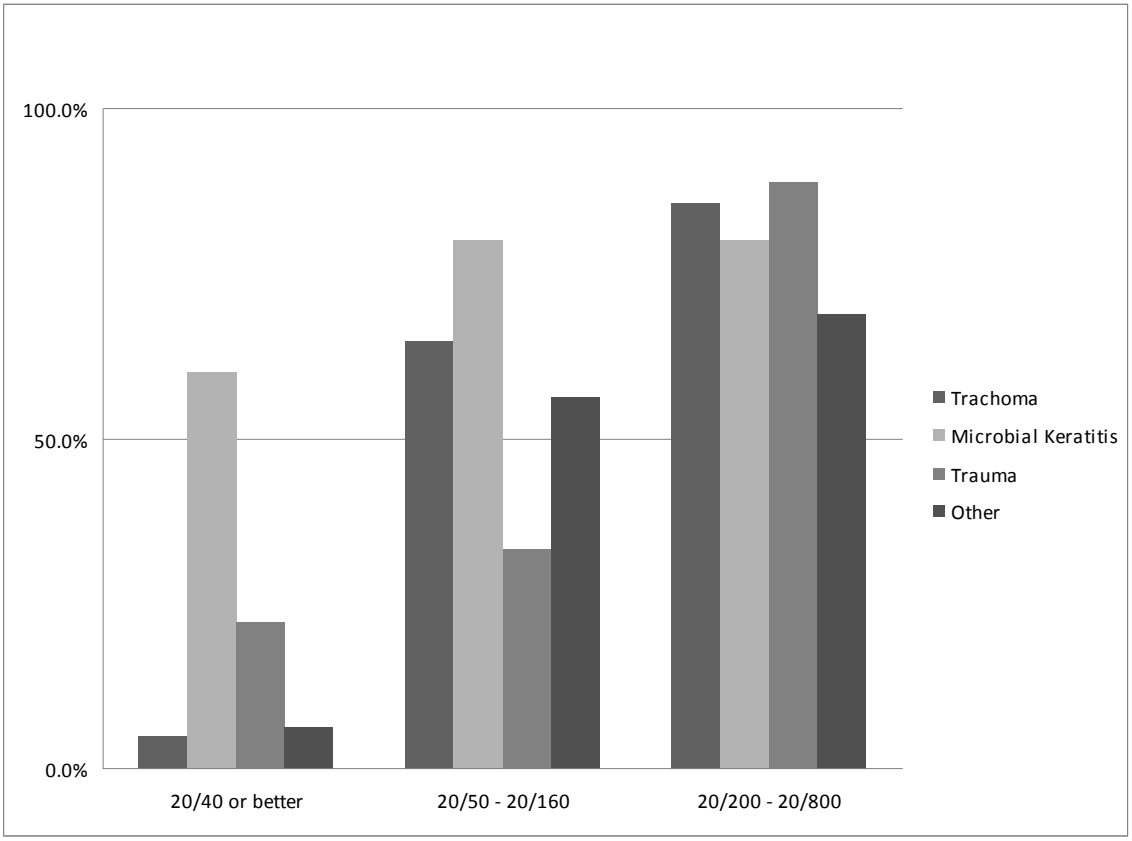
The difference between eyes with trachoma, microbial keratitis, or trauma versus other causes of stromal scarring is significant ($P = 0.02$).

Table 15. Penetrating Keratoplasty for Stromal Scarring: Final Best Corrected Visual Acuity vs Etiology (clear grafts only)

	Trachoma		Microbial Keratitis		Trauma		Other	
Visual Acuity	n	Cum %	n	Cum %	n	Cum %	n	Cum %
20/40 or better	5	4.8	3	60.0	2	22.2	1	6.3
20/50 to 20/160	63	64.8	1	80.0	3	33.3	8	56.3
20/200 to 20/800	22	85.7	0	80.0	3	88.9	2	68.8
CF	9	94.3	0	80.0	0	88.9	3	87.5
HM	4	98.1	0	80.0	1	100.0	2	100.0
LP	1	99.0	1	100.0	0	100.0	0	100.0
NLP	1	100.0	0	100.0	0	100.0	0	100.0
Total	105		5		9		16	

Cum % = cumulative percentage of eyes achieving this level of vision or better; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception.

Figure 31. Corneal Edema: Final Best Corrected Visual Acuity (clear grafts only)



The differences among the surgical subgroups is not statistically significant ($P = 0.58$).

VII. DISCUSSION

The present study provides an excellent opportunity to evaluate the outcome of primary optical PKP performed in a public health service facility of a developing country in which sufficient budgetary support was available for implementation of a national keratoplasty program. The establishment of a modern eye care facility, staffed with well-trained ophthalmologists and ancillary personnel, and the provision of a reliable source of donor tissue and appropriate pharmaceuticals provided the basic ingredients required for implementation of a successful program. The network for patient referral to and from the central care facility and the availability of government-sponsored transportation to and from the hospital provided the access for initial surgical intervention and essential postoperative management. Nonetheless, the critical variable of patients' compliance with the use of postoperative medications and keeping scheduled postoperative visits, as well as their understanding of the signs and symptoms of keratoplasty complications and the necessity of seeking urgent care for management, remained a factor that threatened to compromise the surgical outcomes.

The retrospective nature of this study imposes several inherent limitations. Despite the relative standardization of care at KKESH, a certain degree of variation in the clinical methods of the participating ophthalmologists is inevitable. Different approaches to patient selection, acceptance and allocation of donor tissue offered by the KKESH Eye Bank, graft sizing, suture technique, postoperative corticosteroid regimens, suture removal, and aggressiveness of visual rehabilitation can introduce outcome bias. The precise scheduling of follow-up cannot be ensured in the same manner as that associated with prospective studies, and the absence of measures to ensure maximum retention of the study participants results in incomplete follow-up of many cases. Unlike prospective studies where systematic documentation of key ophthalmic findings is available for statistical analysis, many key features of the ophthalmic examination, which would have been desirable to incorporate into the present study, were excluded because of inconsistent chart documentation. Specifically, the ophthalmic risk factors of ocular

surface disease (aqueous tear deficiency, meibomian gland dysfunction, presence and severity of post-trachomatous conjunctival fibrosis, and presence and severity of climatic droplet keratopathy), peripheral corneal neovascularization (superficial vs deep, number of quadrants, axial extension), anterior and posterior synecchia, serial pachymetry, and serial endothelial cell counts were inadequately documented on the patient medical records; thus, it was necessary to exclude these risk factors from the statistical analysis.

Despite the retrospective nature of the study, many items on the patient medical records could be used to generate reliable and reproducible statistics because they were not subject to documentation deficiencies. These included the dates of surgery, outpatient follow-up visits, ER visits, donor tissue parameters, surgical technique, associated ocular procedures, and major postoperative complications. Although the documented encounter dates provided insights into patients' compliance with scheduled visits and their willingness to seek urgent care, they did not afford an opportunity to evaluate actual compliance with the prescribed medications, nor did they identify the percentage of patients who neglected to attend to acute symptoms. The practice of admitting patients for management of the acute complications of endothelial rejection, bacterial keratitis, and PEDs helped ensure that the variable of compromised compliance with management of these graft-threatening conditions was not applicable. Because the evaluation of graft clarity was done retrospectively, a category of "indeterminate" was not included, requiring that any graft with a loss of central clarity that was associated with visual loss be classified as either "clear" or "failed." The inclusion of borderline cases as "failed" rather than "indeterminate" may have resulted in a slight underestimation of graft survival probability. Conversely, the uncertainty of the actual date of loss of central clarity that occurred between follow-up visits and the use of the date on which the diagnosis of graft failure was documented may have introduced bias toward the overestimation of graft survival probability at any time point. Vision was well documented at each visit, but the diligence that would have been provided by a prospective study with respect to performing careful spectacle and/or contact lens

refractions at designated postoperative intervals was missing and, therefore, may have resulted in an underestimation of the actual visual outcome.

Graft Survival

The 5-year probability of graft survival for primary adult optical PKP at KKESH was slightly better than 80% for procedures performed between 1997 and 2001. These results are comparable to historical series from Western countries in which the 5-year graft survival probability varied from 65% to 90%.[120-131] The relatively broad range of reported survival rates in Western centers is attributable to the statistical inclusion of several categories of high-risk keratoplasty, such as pediatric PKP, therapeutic PKP, and repeat PKP, which were not included in the present analysis. When comparisons were made for specific surgical indications for optical PKP, results at KKESH were comparable to those obtained in Western centers for keratoconus, stromal scarring, and stromal dystrophies but were less favorable for corneal edema.

Keratoconus

The prognosis for PKP in treating keratoconus is excellent because of the avascular nature of this disorder and the performance of surgery on highly motivated, compliant young patients. A 5-year probability of graft survival in excess of 95% is consistently reported in Western countries,[124-145] and similar results were documented in our patient population. However, unlike most Western series, more than 20% of our cases were performed in eyes that also had concomitant VKC, a condition that might have been expected to result in slightly less favorable outcomes because of the additional risk factors of a compromised ocular surface and an increased prevalence of peripheral vascularization.[146-155] Despite the presence of these cases in the surgical mix, the overall 5-year graft survival probability was 96.1% for all eyes with keratoconus, with survival that was slightly better in eyes with concomitant VKC than those in which it was absent.

The similarity in graft survival probability between keratoconic eyes with or without VKC at all time points was applicable to all risk factors that were analyzed, including age at the time of surgery, history of previous hydrops, and occurrence of postoperative complications. There were no significant differences in the overall prevalence of postoperative complications in eyes with or without VKC, nor were any of the postoperative complications significantly associated with an increased risk of graft failure. Grafts in both groups seemed to be resilient to failure after the onset of complications. Only 4.5% of eyes with VKC developed graft failure following the occurrence of a postoperative complication, and only 1.6% of eyes without VKC developed graft failure after the occurrence of a postoperative complication.

The prevalence of immune-mediated endothelial rejection episodes was slightly lower in eyes with VKC compared to those without VKC. There is experimental evidence that the immunological profile of VKC may confer relative protection to the future corneal graft,[150,151] thereby offering a possible explanation for the lower prevalence of rejection episodes in these eyes. The local immune system in eyes with atopic conditions such as VKC tends to be "biased" toward the T-helper 2 (Th2) lymphocytic array of immune cytokines and, thus, directs the immune signal away from the T-helper 1 (Th1) phenotype. The induction and expression of delayed hypersensitivity reactions typically associated with endothelial rejection episodes are therefore inhibited, a factor that may have contributed to the reduced prevalence of this complication.

Concerns that eyes with VKC may be more prone to ocular surface-related complications were confirmed by a statistically significant increased prevalence of late-onset PED. It is my clinical experience that, in contrast to reports in the Western literature, VKC activity persists well beyond the age of puberty in the Saudi population. Despite the fact that all eyes with VKC underwent PKP only after good medical control had been achieved and maintained for a reasonable period of time (usually >6 months), it is not unreasonable to expect epitheliopathy to occur during the postoperative course as a result of reactivation of the disorder. Fortunately, the combination of epitheliopathy and

occasional premature loosening of interrupted sutures secondary to peripheral vascularization did not result in an increased risk of development of bacterial keratitis.

Corneal Edema

With a 5-year probability of graft survival of 40.3%, corneal edema was the surgical indication for PKP with the least favorable outcome in our study population. In addition, this surgical category had the least favorable comparison with results from Western centers.[126-128,156-174]

The greatest disparity in graft survival probability after PKP for corneal edema between Saudi and Western patients was for phakic corneal edema. In Western countries, where phakic corneal edema is much more common because of an increased prevalence of Fuchs' endothelial dystrophy, the 5-year probability of graft survival is usually better than 80%,[126-128,156-160] in contrast to only 33.3% in our patient population.

Irrespective of the setting, aphakic corneal edema is associated with a guarded prognosis for graft survival, with a wide range of reported 5-year probability of graft survival from 45% to 70%,[126-128,161-167] and an even less satisfactory result of 38.2% in the present study.

Eyes with pseudophakic corneal edema are historically reported to have better graft survival than aphakic eyes, with a 5-year probability of graft survival ranging from 45% to 90%.[126-128,168-173] Most series report more favorable results in cases associated with PC IOLs compared to those with AC IOLs. In our patient population, the 5-year graft survival probability in eyes with corneal edema associated with PC IOLs was significantly higher than that in eyes with corneal edema associated with AC IOLs. This difference is probably related to a tendency to insert AC IOLs after complicated cataract surgery, especially when there has been a rupture of the posterior capsule with or without vitreous loss,[175] and for corneal edema to occur in association with multiple

additional complications such as chronic intraocular inflammation and poor control of IOP. The insertion of PC IOLs is usually associated with uncomplicated cataract surgery, with ensuing corneal edema caused in most cases by subsequent endothelial cell loss and attrition, often in the absence of other associated intraocular abnormalities.

Eyes with corneal edema in our patient population and in Western patient populations shared risk factors of similar patient age and previous cataract surgery (in the case of aphakic or pseudophakic edema). However, additional risk factors in Saudi patients seem to contribute toward the further reduction in graft survival. These factors include (1) the necessity of glaucoma surgical intervention prior to PKP in nearly 15% of eyes, (2) the occurrence of one or more postoperative complications in more than 50% of eyes, and (3) a higher prevalence of ocular surface abnormalities than in Western patients because of the ubiquitous presence of sequelae of trachoma in older Saudi patients (notably women) and/or climatic droplet keratopathy (especially in men), as manifest by a statistically significant increased prevalence of PEDs and bacterial keratitis after keratoplasty in these eyes.

Stromal Scarring

The prognosis for PKP in treating stromal scarring is highly variable, depending on the etiology responsible for corneal opacification.[176-182] Most series report results for stromal scarring that is attributed to a combination of traumatic injuries and previous bacterial, fungal, or herpetic keratitis. Stromal scarring that was attributed to these etiologies accounted for only one fifth of the cases performed in our series. The probability of graft survival after PKP in these cases was similar to that reported for the same indications in the Western literature.[176-182]

The present series is unique in that the primary etiology responsible for stromal scarring was trachoma in nearly 75% of eyes. Trachoma has traditionally been considered to have a poor prognosis for successful PKP.[182] It is important to recognize, however, that the spectrum of post-trachoma sequelae ranges from mild corneal scarring, without severe

eyelid and ocular surface disease, to end-stage corneal scarring and vascularization associated with ankyloblepharon and advanced symblepharon. The prognosis for PKP should also reflect a commensurate prognostic spectrum, ranging from good to hopeless. The judicious selection of milder cases, combined with strict attention to correction of eyelid abnormalities (such as trichiasis and entropion), and the aggressive management of ocular surface disease (such as dry eye syndrome and meibomitis) should allow PKP to be performed with a reasonable prognosis for graft survival and good visual outcome for many patients with corneal blindness attributed to chronic trachoma. In a small series of 16 eyes with trachomatous corneal scarring that underwent PKP after dry eye, meibomian gland dysfunction, and eyelid abnormalities had been carefully identified and aggressively managed, Koçak-Midillioglu and associates[178] reported that 87.5% of grafts remained clear after a mean follow-up period of 26.1 months. The 127 cases of PKP performed in the present study for trachomatous stromal scarring constitute, by far, the largest series ever reported for this indication. The overall graft survival rate was 80.3% after a mean follow-up time of 42.1 months. The probability of graft survival was 98.3% at 1 year and 76.6% at 5 years.

As in the smaller series by Koçak-Midillioglu and associates,[178] patient selection was probably the principal reason for the unexpectedly good results in our patient population. The encouraging results were most likely because of the careful selection of patients without significant conjunctival shrinkage, as suggested by the absence of the need for ocular surface reconstruction prior to PKP. Whereas many eyes had received mechanical removal or cryoablation for trichiasis, only 5.6% of eyes required eyelid surgery for trichiasis prior to or at the same time as PKP, and no patients had a subsequent need for eyelid procedures. The relatively low prevalence of late PEDs in only 3.9% of these eyes—none of which were associated with the development of secondary microbial keratitis—supports the claim that ocular surface disease was well controlled.

There was a general tendency to select patients with longstanding corneal scars who experienced recent visual deterioration caused by the progression of senile cataracts.

Cataract surgery was performed during the clinical course in 117 (92.1%) eyes, of which the vast majority of procedures were done at the same time as PKP. As with previous studies,[183-193] the concomitant performance of cataract surgery did not adversely affect graft survival. The few cases of cataract surgery that were done prior to PKP or after PKP in these eyes also did not adversely affect graft survival.

Stromal Dystrophy

As with keratoconus, the prognosis for keratoplasty in treating classic stromal dystrophies is excellent because of the avascular nature of these disorders and the performance of surgery on highly motivated, compliant young patients with minimal ocular surface disease and the absence of other associated ocular abnormalities.[179,194,195] Most reports of PKP for stromal dystrophies are skewed toward the results of dominantly inherited granular or lattice dystrophy, which is much more common worldwide than recessively inherited macular dystrophy. Because of its small gene pool, macular corneal dystrophy is the most common stromal dystrophy in Iceland, where it accounts for 33% of corneal transplants.[196,197] As a result of frequent consanguinity, macular corneal dystrophy is the most common stromal dystrophy in KSA,[198,199] accounting for nearly 90% of PKPs performed for classic corneal dystrophies.[198] In the present study, 100% of PKPs performed for stromal dystrophies were for macular corneal dystrophy.

Reduced access to routine and emergency follow-up care in developing countries has been demonstrated to compromise dramatically the survival of PKPs performed for stromal dystrophies. In India, Rao and associates[179] and Pandrowala and associates[195] reported 5-year probability of graft survival of 56% and 74%, respectively, and attributed this deviation from Western reports to the presence of logistical barriers to access to follow-up care. In a recent report from our institution, the prognosis for PKP in treating macular corneal dystrophy over a 20-year period was found to be excellent, yielding a 5-year probability of graft survival of 89.8%.[200] The wide geographic

distribution of patients did not seem to affect graft survival adversely. In the present series of patients who had surgery between 1997 and 2001, the 5-year graft survival probability was 85.9%. Once again, the geographic distribution of the patients and compliance with postoperative visits were not factors in graft survival.

Country-specific Risk Factors vs Graft Survival

Country-specific risk factors affecting corneal graft survival are those that are unique to, or influenced by, the health care system where the procedures are performed. These include geographic, logistical, socioeconomic, cultural, and religious factors that influence patient access not only to preoperative evaluation and surgical intervention in sophisticated ophthalmic facilities with well-trained personnel but also to the meticulous postoperative care that is critical for maintenance of graft clarity. In the present study, demographic variables unique to KSA did not significantly affect the probability of graft survival. Differences in the provision of corneal donor tissue may vary considerably between Western and developing countries with respect to the availability of fresh donor tissue and the requirement of importing tissue, thereby inducing potential graft-compromising risk factors associated with shipment and delays in utilization. Increasing donor age was significantly associated with an increased risk of graft failure in both univariate and multivariate analyses, whereas endothelial cell count, death-to-preservation time, and preservation-to-surgery time were not.

Demographic Variables

During the study period, Saudi patients had the benefit of receiving government-subsidized keratoplasty from corneal fellowship-trained surgeons, who were equally represented by board-certified American and Saudi ophthalmologists, at KKESH, a state-of-the-art facility.

It is not possible to determine directly from the available data the percentage of eligible patients who entered the keratoplasty referral and surgical system. However, it is not

unreasonable to hypothesize that most patients with corneal disability who were motivated to undergo surgical intervention had the opportunity to receive treatment. Similar to the situation in Western countries, it is likely that most young patients with corneal disability and educational or occupational needs for better vision were eager to pursue keratoplasty options. However, there are several sociocultural reasons that the demand for keratoplasty might be reduced in females compared with their male counterparts. Because women are not allowed to drive in KSA, mild visual impairment that would tip the balance toward requesting surgical intervention in a male patient might result in a more conservative approach in a similarly impaired female patient. Women must be accompanied to and from physician visits by a close male relative, which creates a de facto need to obtain authorization, a factor that might result in fewer grafts being performed because of "permission bias." Finally, there are still fewer women than men in the labor force, thereby reducing occupational requirements for better vision.

In younger patients, there did not seem to be any evidence of substantial gender bias in surgical intervention for keratoconus or stromal dystrophy. Although males accounted for 61% of patients who underwent PKP for keratoconus, a similar predominance of male patients has routinely been reported in many published series, suggesting that gender differences in prevalence rather than patient selection bias account for the disparity.[126-128,133-145] There was no evidence of early intervention bias attributable to greater driving and/or occupational needs by male patients. Both male and female patients had a median preoperative vision of 20/800, and females were slightly more likely than males to have surgery performed when the preoperative vision was 20/60 or better (4.4% vs 3.5%, respectively). With respect to the autosomal recessive disorder of macular corneal dystrophy, which is equally represented in the Saudi population, male patients accounted for 53% of cases. The slightly better median preoperative visual acuity in male patients (20/160 vs 20/200), as well as the slightly higher percentage of male patients with a preoperative acuity of 20/60 or better (4.5% vs 2.6%, respectively),

suggests that early intervention bias may have been responsible for the slight gender differences for PKP in treating this disorder.

Among older patients, decreased driving and occupational demands would proportionally reduce the demand for keratoplasty, with the anticipated creation of a larger gender gap attributable to a much smaller representation of older Saudi women in the labor force than of younger women. Male patients accounted for 72% of PKPs performed for aphakic or pseudophakic corneal edema. The gender bias in this group is indicative of not only the original bias in performing cataract surgery in a higher percentage of men but also a greater tendency to offer additional surgical intervention to men with poor surgical results. Although women accounted for 52% of PKPs performed for trachoma and 45% of PKPs performed for phakic corneal edema, these percentages are far below their representation of these disorders in the general population, where more than 75% of patients with visual disability related to trachoma[12-14,20,21] and 60% with impaired vision related to Fuchs' endothelial dystrophy are women.[126-128,152-160]

There were legitimate concerns that the distribution of the post-PKP population over a larger geographic area would be reflected in reduced compliance with postoperative visits, especially among women and older patients, and that this might result in decreased graft survival because of delays in diagnosis and treatment of postoperative complications. However, there were no significant differences in the probability of graft survival attributable to geographic location, with residents outside the central region having slightly better overall graft survival probability than those from the central region. There were also no significant gender differences, although women had slightly better graft survival probability than men.

There were concerns that logistical barriers for women, because of the mandatory requirement of being accompanied by a close male relative when traveling, might compromise postoperative visit compliance. Although a higher percentage of women kept 100% of their visits than men, a lower percentage also kept less than 80% of their

visits. Furthermore, there was a significant difference in the likelihood of women from outside the central region keeping less than 80% of visits compared with those in the central region. The absence of statistically significant differences in graft survival associated with the poorer visit compliance of non-central region women probably represents a "reluctance to travel bias," in which patients who are doing well tend to skip visits, whereas those who are more symptomatic are more motivated to keep their appointments. Similarly, the slight tendency for older patients from both the central and non-central regions to keep less than 80% of their scheduled visits than their younger counterparts was not significantly associated with decreased graft survival.

The remarkable number of unscheduled ER visits by our patients presents a compelling argument that the public health system of KSA provided an excellent backup mechanism for dealing with contingencies arising between scheduled visits and that patients were motivated to take advantage of this opportunity. Unlike the ease with which patients in Western countries can usually contact their ophthalmologists and be seen as "drop-ins" on short notice in a regular office setting, patients treated at KKESH do not have a simple mechanism for arranging unscheduled visits to the outpatient clinic. Fortunately, there is a well-staffed, around-the-clock ER facility at the hospital, which provides all postoperative patients with unlimited access to interim examinations, and all postoperative PKP patients are specifically instructed to present to the ER for any subjective symptoms suggestive of a possible complication.

Overall, one or more visits to the ER were made in conjunction with more than 60% of the cases. More than 10% of cases were associated with 10 or more unscheduled visits. A higher percentage of women were seen in the ER than men, suggesting that when symptoms were present, there was no reluctance on the part of patients to seek care and on the part of the male relatives to provide transportation and to accompany the patient to the hospital. Residents from outside the central region had only a slightly lower prevalence of unscheduled visits to the ER than those from the central region, suggesting that geographic distance was not a major obstacle to seeking urgent care, when

necessary. Among patients who required one or more visits to the ER, overall graft survival was significantly reduced, but it was still better than 80%. Whereas this increased likelihood of graft failure is probably multifactorial, the most logical explanation is that there is a selective bias toward patients with problematic grafts seeking emergent attention. Although definitive proof is not possible to attain regarding the fate that would have befallen these eyes in the absence of acute intervention, there is little doubt that many of these grafts would have failed if access to urgent care had not been available and if patients had not been so willing to seek urgent care for acute symptoms.

Donor Tissue Variables

The highly successful nature of PKP is absolutely dependent upon the availability of suitable donor tissue. The initial rate-limiting step in obtaining a clear graft is the transfer of sufficient viable donor endothelium to the recipient to establish initial graft clarity.[25] Long-term graft clarity and visual function require the maintenance of sufficient viable endothelium, despite the inevitable attrition that occurs because of aging, subsequent surgical procedures, and post-PKP complications.[201-219]

Since the inception of keratoplasty services in KSA and at KKESH, there has been almost complete dependence on imported donor tissue, despite concerted efforts to develop a local donor network.[1] In the present study, imported tissue was used for 885 (97.3%) cases. Fortunately, the ability to preserve donor tissue in Optisol storage media at 4°C for up to 14 days with little loss of endothelial viability[220-228] offers the possibility of successfully using internationally acquired tissue in countries with inadequate supplies of local tissue but with sufficient budgetary capabilities to support the considerable costs associated with processing and shipping fees, which range from US $1200 to US $1800 per case. Although imported donor tissue meets EBAA requirements, there are some concerns that there may be some distribution bias toward exporting tissue that is at the upper limit of the requirements for age and death-to-

preservation time and at the lower end for ECD. There are additional concerns about the prognosis for short-term and long-term survival associated with internationally acquired tissue because of the potential loss of ECD and viability secondary to inconsistent refrigeration and prolonged preservation-to-surgery time.[25,68-70,115,229-232]

Although studies have demonstrated excellent endothelial survival after international shipment of donor tissue,[229] and excellent short-term and long-term survival have been reported in centers that rely heavily on internationally acquired tissue,[25,86,99,104,200,233] there have been insufficient numbers of cases analyzed to determine which, if any, donor factors may be associated with an increased risk of graft failure. Because more than 95% of our cases were performed with tissue obtained from EBAA-certified eye banks in the United States, the large number of cases in the present study affords the opportunity to analyze the impact of donor age, ECD, death-to-preservation time, and preservation-to-surgery time of internationally acquired donor tissue on graft survival probability in relatively low-risk PKP.

The greatest concern about the use of internationally acquired tissue is the increased preservation-to-surgery time that inevitably occurs during the acquisition, processing, and transfer of tissue between the United States and KSA. There are conflicting reports in the literature with respect to increased preservation-to-surgery time and the probability of graft survival. Hu and associates[25] found a significant correlation between prolonged storage (>7 days) in Optisol media and increased risk of graft failure; however, this outcome may have been as a result of the use of this tissue for high-risk keratoplasty. In a series of low-risk PKP with a similar distribution of surgical indications as the present study, Doganay and associates[231] found no correlation between increasing preservation-to-surgery time and graft survival probability. A previous study of all PKPs performed in 1999 at KKESH also found no correlation between increased preservation-to-surgery time and graft survival probability.[228]

One of the most striking findings of the present study is that preservation-to-surgery time was the least significant donor risk factor with respect to the probability of graft survival. One hypothesis is that there is no substantial loss of endothelial function during the first 2 weeks of storage in Optisol media, as suggested by in vitro studies.[220-226] However, it is unreasonable to expect that no loss of endothelial viability occurs with progressively longer periods of storage. Some studies have suggested that preservation-to-surgery times of more than 7 days may be associated with decreased survival of major histocompatibility (MHC) class II-positive dendritic cells,[234] which may result in a compensatory mechanism of decreased endothelial rejection episodes that offsets the loss of endothelial viability associated with prolonged storage.[235] Although we did not observe any correlation between prolonged storage and fewer documented rejection episodes, we cannot discount the possibility that fewer subclinical endothelial rejection episodes occurred in eyes with prolonged storage and may have played a compensatory role in offsetting the presumptive adverse effect of prolonged storage on endothelial viability.

One problem associated with the necessity of utilizing internationally acquired donor tissue and its associated prolonged storage time was the inevitable presence of total or near-total postoperative epithelial defects in all of the grafts in this study, including 2.0% that persisted for at least 14 days. Previous investigators have documented this correlation between prolonged storage and postoperative epithelial defects.[222,236,237] Machado and associates[237] demonstrated that the epithelial status on the first postoperative day is not predictive of the 1-month status of the ocular surface or the likelihood of graft survival, an observation supported by the present study in which there was no significant correlation between the length of time required for reepithelialization and the probability of graft survival.

Prolonged storage time did not seem to be related to an increased rate of primary graft failure or endophthalmitis. The bacterial contamination rate of donor tissue rims was 19.4%, which is well within the range reported from similar cultures obtained in Western

series where storage times were much shorter.[238-241] The only case of culture-confirmed bacterial endophthalmitis was not associated with a contaminated donor rim. Although fungal contamination of the donor rim is often associated with early-onset and late-onset fungal keratitis and/or endophthalmitis,[68-70,242,243] this did not occur in any of the 6 fungal-contaminated donor rims in the present study.

One of the most disturbing features of the present study was the finding that increasing donor age is significantly associated with a decreased probability of graft survival on both univariate and multivariate regression analyses. This effect was independent of death-to-preservation time, surgery-to-preservation time, and ECD. The correlation between increasing donor age and decreased graft survival probability was present for all surgical indications but was most pronounced in eyes with corneal edema, where it was statistically significant. Although not statistically significant, increasing donor age was associated with an HR that was greater than 1.0 for the other surgical categories.

Although multiple studies have demonstrated no correlation between donor age and the probability of graft survival,[244-249] and two studies have advocated the safety and efficacy of "older" (>66 years)[248] and "very old" (≥85 years)[249] tissue, several caveats are necessary before adopting an "age does not matter" mantra with respect to all cases of PKP. In addition to the findings in our patient population, several other investigators have found that increasing age may be associated with an increased risk of graft failure.[44,99,215,250] Therefore, compensatory factors that may have contributed to a lack of correlation between age and graft survival probability in some studies may not be applicable to every patient population and situation. The progressive disparity in the probability of graft survival demonstrated in this study between eyes that received younger donor tissue and those that received older donor tissue supports the hypothesis that differential survival is correlated with differential long-term endothelial survival. Some authors believe that older tissue may be less antigenic and may be associated with fewer endothelial rejection episodes, thereby offsetting the anticipated adverse impact of reduced endothelial viability on graft survival.[251] Palay and associates[247] reported that, in

eyes with comparable graft survival, a significantly increased risk of endothelial rejection episodes occurred with the use of donor tissue between 0 and 5 years of age than with the use of donor tissue between 40 and 70 years of age. Al-Rajhi and Wagoner[99] observed that, in eyes with congenital hereditary endothelial dystrophy, the use of donor tissue less than 5 years of age was associated with significantly reduced graft survival probability compared with the use of donor tissue between 5 and 30 years of age. However, they also reported a decreased probability of graft survival if donor tissue was older than 30 years. In the present study, there was a increased, rather than reduced, prevalence of endothelial rejection episodes in older patients, thereby offsetting the theoretical immunological advantages associated with the use of older donor tissue.

The poor outcomes that occurred with the use of older donor tissue in patients with corneal edema are probably attributable to the cumulative "triple threat" posed by the following: (1) reduced donor endothelial viability,[251] (2) compromised peripheral recipient endothelium,[252-254] and (3) inherent risks associated with increased recipient age.[9,211,253] Although no morphological studies were performed on the donor tissue used in our cases, a previous study by Miyata and associates[251] found a significant correlation between increasing donor age and morphological variation of human cultured endothelial cells obtained from donor tissue. Reinhardt and associates[252] demonstrated an accelerated endothelial cell loss, which was independent of immunological loss, after PKP in eyes with corneal edema compared to those without preoperative endothelial dysfunction. They attributed this finding to the peripheral migration of relatively healthier transplanted endothelium. Finally, Musch and associates[211] found a synergistic correlation between increasing donor and recipient age and accelerated endothelial cell loss during the first postoperative year. As previously discussed, a number of additional risk factors in eyes with corneal edema accounted for the poorer results in Saudi patients compared with those in Western countries in whom the same triple endothelial threat to graft survival was also applicable, but in whom it does not seem to pose the same grave threat to graft survival that it does in our patient population.

Universal Risk Factors vs Graft Survival

Universal risk factors that affect graft survival probability are those that are inherent in the procedure itself and can be expected to occur independently of the location in which the surgery is performed.[44,243,255-259] These factors include surgical variables and postoperative complications. In Western countries, the adverse impact of universal risk factors has been minimized by reducing or eliminating country-specific factors, such as barriers to access to routine and emergent postoperative care. This is not necessarily the case in developing countries where impaired access, in association with commonly occurring postoperative complications, may greatly increase the risk of graft failure. In the present study, recipient graft size was the only surgical variable that was significantly associated with graft survival on both univariate and multivariate analyses.

Surgical Variables

Surgical indication was the most important surgical variable affecting the probability of graft survival. Five-year graft survival probability ranged from a high of 96.1% for keratoconus to a low of 40.3% for corneal edema. Compared to eyes with keratoconus, eyes with stromal dystrophy, stromal scarring, and corneal edema had a 4-fold, 8-fold, and 22-fold increased risk of graft failure, respectively.

Increasing patient age was significantly associated with an increased risk of graft failure on univariate, but not multivariate, analysis. The dramatic reduction in graft survival probability among patients older than 60 years of age was multifactorial, but the predominance of the relatively poorer prognostic surgical category of corneal edema and stromal scarring, and the scarcity of the better prognostic groups of keratoconus and stromal dystrophy among older patients, was the most likely source of statistical bias in the univariate analysis. In addition to the surgical indication, the age-related risk for graft failure was attributable to the increased prevalence of ocular comorbidity in older patients, such as ocular surface disorders (especially in patients with stromal scarring) and decreased baseline endothelial function (especially in patients with corneal edema).

Unexpectedly, it did not seem to be related to compliance with postoperative visits because older patients had comparable compliance with that of younger patients.

Within the range of graft size used for optical PKP, there was an inverse correlation between graft size and graft survival probability, which was statistically significant on both univariate and multivariate regression analyses. This was especially true if the graft size was less than 7.0 mm, in which case the 5-year probability of graft survival was reduced to 58.1%. Inasmuch as the graft sizing was not randomized, it is possible that bias may have been introduced so that graft size was just a surrogate marker for other factors that actually were causally related to the probability of reduced survival. One possibility is that smaller graft size was preferentially selected in relatively poorer prognostic cases with peripheral vascularization, thereby accounting for the observed findings. The data do not, however, support this hypothesis because the statistical correlation between graft size and probability of graft survival was identical for keratoconus and stromal scarring, with vascularization being relatively absent from the former and common in the latter.

Graft failure attributable to chronic endothelial attrition in response to cell loss caused by aging, immune-mediated rejection, and peripheral endothelial migration should occur earlier in smaller grafts because of the more rapid depletion of the critical ECD required to maintain graft clarity. This hypothesis is supported by the finding that smaller graft size was associated with decreased survival in all surgical categories but was more pronounced in eyes with corneal edema, where the peripheral migration of relatively healthy donor endothelium further depletes the central ECD.[242] Among eyes that experienced immune-mediated rejection episodes, graft survival probability was poorer in smaller grafts in this and previous studies from our institution.[260]

Although preexisting glaucoma per se may not be a risk factor for graft failure, the need to perform glaucoma surgical procedures at any point in the clinical course to provide adequate IOP control is usually associated with an increased risk of graft failure.[247,261-283]

There is some evidence that trabeculectomy with mitomycin C may be associated with a better probability of graft survival than shunt procedures; however, glaucoma control may not be as good.[267,271,272,283] In the present study, the ubiquitous presence of chronic ocular surface disease in older patients, which was often associated with conjunctival fibrosis, resulted in shunt procedures, rather than trabeculectomy, being utilized for surgical management of glaucoma in over 90% of the cases. Glaucoma surgical procedures performed before, during, or after PKP were significantly associated with a higher risk of graft failure on univariate, but not multivariate, analysis. In all likelihood, the need to perform glaucoma procedures at any time in the clinical course was an important clinical risk factor affecting graft survival probability, but we were unable to establish statistical significance because of the relatively small number of cases and the exclusive sequestration of these cases to the surgical indications of corneal edema and stromal scarring.

Irrespective of the type of glaucoma procedure, there are contradictory reports in the literature regarding the relationship between timing of glaucoma surgical procedures and graft survival probability.[262-267,271-273,276] Whereas some previous studies have suggested that glaucoma surgical procedures performed prior to or at the same time as PKP may be associated with a lower risk of graft failure,[276] the present study found just the opposite. Glaucoma procedures performed before, at the same time, or after PKP were associated with a 5-year probability of graft survival of 19.0%, 50.0%, and 66.6%, respectively.

Previous and concomitant, but not subsequent, cataract surgeries were significantly associated with an increased risk of graft failure on univariate, but not multivariate, analysis. In all likelihood, the prior, simultaneous, or subsequent need to perform cataract surgery in these cases was not clinically important. The adverse outcomes were almost completely attributable to the high prevalence of cataract-associated graft failure in the relatively poorer prognostic categories of aphakic and pseudophakic corneal edema. By definition, all eyes with aphakic or pseudophakic corneal edema had prior cataract surgery; therefore, it was not possible to evaluate independently the risk

associated with the surgical indication from that associated with previous cataract surgery. Previous studies have failed to identify an increased risk of graft failure if cataract surgery is performed before,[161] during,[158,168,188] or after PKP[167,184,191] in eyes with phakic corneal edema, stromal scarring, keratoconus, and stromal dystrophy. The current study also failed to find any additional risk for these surgical indications.

The combined suture technique was associated with a significantly better probability of graft survival than the interrupted technique on univariate, but not multivariate, analysis. This finding is easily explained by the tendency to use the combined suture technique in eyes without vascularization and with a favorable prognosis (especially those with keratoconus and stromal dystrophy) and to use the interrupted suture technique in eyes with vascularization and a less favorable prognosis (especially those with corneal edema and stromal scarring).

Complications

Postoperative complications are quite common after PKP and pose a substantial risk to the probability of graft survival,[260-315] especially if they are not identified and treated in a timely manner. In the present study, one or more major complications were documented in nearly 40% of eyes undergoing primary adult optical PKP. A significantly higher prevalence of post-PKP complications was associated with corneal edema and stromal scarring than with keratoconus and stromal dystrophy. Although the prevalence of postoperative complications was comparable, graft failure occurred more frequently in eyes with corneal edema than in those with stromal scars. Despite a lower prevalence of complications, eyes with stromal dystrophy had poorer graft survival probability than those with keratoconus.

Immune-mediated endothelial rejection episodes, a complication unique to PKP, are the most frequently reported postoperative complication.[260,284-290] In the present study, endothelial rejection episodes were the most common postoperative complication, with an overall prevalence of 17.3%. They were significantly more common in eyes with

corneal edema or stromal scarring than in those with keratoconus or stromal dystrophy. Although the retrospective nature of this study did not permit the precise determination of the prevalence and severity of corneal vascularization, eyes with corneal edema or stromal scarring undoubtedly had a higher prevalence of corneal vascularization than those with keratoconus or stromal dystrophy, thereby potentially contributing to the increased risk of development of this complication. Chronic trachoma is often associated with peripheral corneal vascularization, and this condition was the primary etiology of corneal opacification in over 70% of the eyes with stromal scarring. Previous trachoma was also present in many other eyes with stromal scarring in which it was not the major etiology of the central corneal opacification, as well as in many eyes with corneal edema. The occurrence of peripheral vascularization in chronically inflamed eyes with aphakic or pseudophakic corneal edema is also well established. Conversely, peripheral corneal vascularization is generally absent in eyes with stromal dystrophies and in those with keratoconus, unless the clinical course has been complicated by hydrops[147,155] or concomitant VKC.[149]

Glaucoma worsening is the leading cause of irreversible visual loss after penetrating keratoplasty attributable to optic nerve damage.[247,261-283] In the present study, glaucoma worsening had an overall prevalence of 15.5%. It was significantly more common in eyes with corneal edema or stromal scarring than in those with keratoconus or stromal dystrophy. Among eyes with corneal edema or stromal scarring, a statistically significant correlation existed between increasing age, the prevalence of preexisting glaucoma, and the presence of aphakia or pseudophakia and the development of glaucoma worsening. The significant differences in these predisposing risk factors in eyes with corneal edema or stromal scarring compared to those with keratoconus or stromal dystrophy may account for the significantly increased prevalence of glaucoma worsening in these surgical categories.

The risk of corneal infection increases dramatically following PKP because of the presence of sutures, which may loosen or break in the interim between postoperative

visits, the presence of relative corneal anesthesia, the use of topical corticosteroids, and the occurrence of persistent epitheliopathy and/or PEDs caused by preexisting ocular surface disease and the use of topical medications, especially glaucoma drops.[47,148,247,248,291-305] In the present study, bacterial keratitis was significantly more likely to occur in eyes with stromal scarring or corneal edema than in those with stromal dystrophy or keratoconus. Because there were no significant differences in patient compliance with postoperative visits between older and younger patients, it is likely that differences in the prevalence and severity of ocular surface disease were the major contributing factors for these differences. Not unexpectedly, the shift from stromal scarring to keratoconus as the predominant indication for PKP over the past 2 decades at our institution has contributed to a reduction in the overall prevalence of post-PKP bacterial keratitis from 11.9% in the 1980s[303] to 5.8% in the present study.

Because of the presumptive higher burden of ocular surface disease, it is not surprising that either a PED or bacterial keratitis occurred in the postoperative course of 13.7% of eyes with stromal scarring and 12.3% of eyes with corneal edema. Nor is it surprising that PEDs or bacterial keratitis occurred in more patients with keratoconus than in those with stromal dystrophy (7.6% vs 2.4%, respectively; $P = 0.10$) because of the presence of VKC in 80 eyes with keratoconus and in no eyes with stromal dystrophy. Among eyes with keratoconus, PEDs were significantly more common in eyes with VKC (6.3% vs 1.0%; $P = 0.04$).

Wound dehiscence is a serious complication that may lead not only to graft failure but also to irreversible visual loss when associated with the extrusion of intraocular contents and the development of retinal detachments.[306-315] This is particularly true in young, active individuals who are more likely to sustain accidental blunt trauma than older, more sedentary patients. In contrast to reports from Western centers,[306-315] the present study found only a slight increase in wound dehiscence in younger patients. It is possible that socioeconomic, cultural, and religious factors that result in the decreased participation of young Saudis in manual labor, contact sports, and alcohol-related

physical altercations may have contributed to the similar prevalence of wound dehiscence as the older patients in this series.

The occurrence of one or more complications was associated with a significantly increased risk of graft failure for the entire study group on univariate, but not multivariate, analysis. This lack of statistical correlation was most likely because of the variation in complication-associated graft failure between the surgical groups. The greatest vulnerability to complications occurred in eyes with corneal edema, where there was a significantly increased risk of graft failure on both univariate and multivariate analyses. The least vulnerability to complications was in eyes with keratoconus, where complications were actually associated with a decreased risk of graft failure.

The specific complications of endothelial rejection episodes, glaucoma worsening, bacterial keratitis, and PEDs were significantly associated with an increased risk for graft failure among the entire study group on univariate analysis. However, there was considerable variability within each of the surgical groups with respect to vulnerability to experiencing graft failure in association with each specific complication.

Differences in the susceptibility to graft failure in conjunction with endothelial rejection episodes may be attributable to differences in the status of the peripheral recipient corneal endothelium caused by aging, disease, or surgical trauma. As previously discussed, peripheral migration of relatively healthy donor endothelium into the corneal periphery in eyes with corneal edema may contribute to initial endothelial depletion, which may be additionally aggravated by further attrition associated with immune-mediated rejection. Conversely, analogous central migration of relatively healthy peripheral recipient endothelium in young patients with keratoconus and in those with stromal dystrophy may contribute to initial endothelial augmentation and ameliorate attrition associated with immune-mediated rejection.

In a similar age population, graft failure occurred in 82.5% of eyes with corneal edema and endothelial rejection episodes, compared to only 32.3% of eyes with stromal scarring—a difference that may be attributable to better peripheral corneal endothelium in the latter. Graft failure occurred in 30.8% of eyes with stromal dystrophy and endothelial rejection episodes, compared to no cases of graft failure in eyes with keratoconus. These differences in graft failure may be attributable to age-related differences in the relative health of the recipient corneal endothelium of eyes in which the endothelial rejection episodes occurred. Most patients with keratoconus were under 25 years of age, and only 3.0% were over the age of 40 years. In contrast, most patients with stromal dystrophy were over the age of 25 years, and 20.5% were over the age of 40 years. All but one case of endothelial rejection-associated graft failure occurred in patients over the age of 40 years. Additional support for the hypothesis that endothelial rejection episode-associated vulnerability to graft failure is related to the status of the peripheral recipient endothelium comes from the observation that similar rates of graft failure occurred in older patients with stromal dystrophy and in those with stromal scarring, in which comparable amounts of age-related endothelial attrition would have been expected to have taken place prior to PKP.

Bacterial keratitis and PEDs were more likely to be associated with graft failure in eyes with stromal scarring than in the other surgical groups, a finding that may have been related to the higher burden of preexisting ocular surface disease in these eyes. Glaucoma worsening was more likely to be associated with graft failure in eyes with corneal edema, a finding that may be have been related to the significantly higher prevalence of preexisting glaucoma in these eyes.

Visual Acuity

The primary purpose of keratoplasty programs is the rehabilitation of patients with corneal blindness; thus, the ultimate measure of success of corneal transplantation is

visual outcome. Surgical intervention was highly successful in providing improved vision for most of the Saudi patients treated in their public health service system. Visual results were excellent for patients with keratoconus and those with stromal dystrophy, and satisfactory for patients with stromal scarring; however, they were disappointing for those with corneal edema. Eyes with keratoconus and those with stromal dystrophy were significantly more likely to achieve a BCVA of 20/40 or better than eyes with corneal edema and those with stromal scarring. Conversely, eyes with stromal scarring, and especially those with corneal edema, were significantly more likely to have a BCVA of 20/200 or worse.

The establishment and maintenance of a clear graft are rate-limiting steps in offering the potential of visual success; however, they do not guarantee a good visual outcome.[188,316] This is particularly true in pediatric patients, where deep amblyopia may be present, and in older patients with concomitant factors (such as persistent epitheliopathy, cystoid macular edema, diabetic retinopathy, and glaucomatous optic atrophy) that may limit vision. Even in the absence of vision compromising ocular comorbidity, unsatisfactory visual results may occur because of high refractive errors, particularly irregular astigmatism. Many of these patients choose to function with no correction or reduced correction, rather than resorting to the more visually satisfying alternative of rigid gas permeable hard contact lenses because of the logistical difficulties associated with numerous trips to the clinic for fitting and modification of lenses, as well as discomfort associated with lens wear in the extremely hot, dry, and dusty environment of the Kingdom.

There was a strong correlation between graft clarity and a good visual outcome in eyes with stromal dystrophy and in those with keratoconus, with approximately 75% of eyes in both groups achieving a BCVA of 20/40 or better in association with a clear graft. In the presence of a clear graft, no eyes with stromal dystrophy and only 1.2% of eyes with keratoconus had a BCVA that was 20/200 or less.

Excellent visual outcome after PKP for keratoconus has been well documented in Western series[126-131] and in developing countries.[176,182] In the present study, visual acuity of 20/40 or better was obtained in 72.4% of eyes, with comparable outcomes between eyes with and those without VKC. Minor differences between this series and some Western series in terms of the percentage of eyes that were 20/40 or better can be easily explained by the relative lack of demand for postoperative contact lens fitting to maximize visual acuity, as well as the relatively infrequent surgical modification of post-keratoplasty refractive errors at our institution during the study period.

Like keratoconus, excellent visual outcomes after PKP have been well documented for stromal dystrophies in both Western series[194] and developing countries[176] if a clear graft is maintained. In the present study, where macular corneal dystrophy was the only "classic" dystrophy that was represented, a BCVA of 20/40 or better was obtained in 63.9% of eyes.

In eyes with corneal edema and in those with stromal scarring, a clear graft was a minimum requirement—but not necessarily a guarantee—of a good visual outcome.[126-128,156-178] Among eyes with corneal edema, there were no significant differences in graft survival between eyes with phakic and aphakic or pseudophakic corneal edema, and no significant differences in visual outcome when all cases were included in the statistical analysis. However, when only clear grafts were analyzed, eyes with phakic corneal edema had significantly better visual outcomes, suggesting that differences in ocular co-morbidity between these two subgroups were visually significant. In contrast, the visual outcome in eyes with stromal scarring that was attributed to previous trachoma, microbial keratitis, or trauma was significantly better than that achieved in eyes with other (and, presumably, mostly herpetic) etiologies for the stromal opacity. This difference was attributed to the significant difference in graft survival that existed between these subgroups. When only clear grafts were analyzed, there were no significant differences in visual outcome between these subgroups, suggesting similar levels of comorbidity.

Uniformly good visual results have been reported in Western centers after PKP for phakic corneal edema, either alone or in conjunction with concomitant or sequential cataract extraction and IOL insertion.[126-128,156-160] These results are attributed to a high probability of graft survival, combined with a low prevalence of preexisting macular or optic nerve disease in most patients. Differences in visual outcome between Saudi and Western patients can be explained almost exclusively on the basis of differences in graft survival probability. Overall, only 45.5% of eyes with phakic corneal edema had a BCVA that was better than 20/200, but this percentage improved to 82.4% among eyes with clear grafts.

Published series of PKP for aphakic or pseudophakic corneal edema invariably report a substantial number of patients with a final visual acuity of 20/200 or worse, which was attributable to persistent macular edema that developed in most cases prior to surgical intervention with PKP, with or without IOL exchange or secondary insertion.[126-128,156-174] Even in the presence of a clear graft, vision that is 20/200 or less occurs in 19% to 36% of eyes. In the present series, the visual outcome after PKP for this indication was poorer than that reported in the literature, which may be explained by several factors, including a much higher rate of graft failure, a higher prevalence of preexisting glaucoma and glaucoma worsening after surgery, and a higher prevalence of diabetic maculopathy in elderly patients in our population. Overall, only 27.1% of these grafts had a BCVA that was better than 20/200, and this percentage improved to only 45.5% among clear grafts, with almost identical results in eyes with corneal edema associated with aphakia, AC IOLs, or PC IOLs. This outcome was substantially less than historical reports, where up to 80% of clear grafts for this surgical indication were associated with vision that was better than 20/200,[126-128,156-174]suggesting that, in addition to the anticipated prevalence of cystoid macular edema, there was probably an important contribution of diabetic retinopathy and glaucomatous optic atrophy toward the poor visual outcomes.

There were insufficient cases of stromal scarring in our series attributable to previous microbial keratitis, trauma, or presumed herpetic disease to permit adequate comparisons

of visual outcomes between our patients and those in previously published Western series. However, there were substantially more cases of post-trachomatous scarring in our series to provide insight into the visual outcome that can be achieved after PKP in well-selected patients with visual disability caused by this disorder. Whereas only a small percentage of patients achieved a BCVA of 20/40 or better, visual acuity that was better than 20/200 was obtained in 56.7% of eyes. Among clear grafts, this outcome improved to 64.8%. Overall, visual acuity improved in 84.3% of eyes, remained the same in 9.5% of eyes, and worsened in only 6.3% of eyes.

Recommendations

Despite the success of PKP that has been achieved in KSA, several specific recommendations can be made to increase the opportunity for attaining even better outcomes in our patient population.

1. Keratoplasty services should be decentralized so that regional programs, similar to the one described at KKESH, can be created. Although the need for patients outside the central region to utilize air transportation to travel to KKESH for initial evaluation, surgical intervention, and postoperative care was not significantly associated with a decreased probability of graft survival, considerable government expense and patient time and inconvenience were required to achieve good graft outcomes for patients distributed over a large geographic area. Because the KKESH fellowship program has successfully trained over 100 cornea subspecialists, it is no longer necessary to concentrate all keratoplasty services in a central facility. The reallocation of resources and personnel to specifically designated regional keratoplasty centers can be accomplished without substantial additional cost, particularly with the savings obtained by eliminating government-subsidized air transportation for patients and their traveling companions to the central facility. KKESH can still meet the keratoplasty needs of the

central region, and serve as a referral source from the regional centers for high-risk keratoplasty.

2. Despite the documented success of utilizing internationally acquired tissue, the KKESH Eye Bank should make a concerted effort to increase local donor awareness and tissue acquisition, thereby reducing, or even eliminating, the very high processing costs associated with the use of imported tissue. The achievement of liver and kidney organ transplantation programs clearly demonstrates that donor programs can be successfully developed within the social and religious environment of the Kingdom.

3. Corneal specialists in KSA should aggressively continue to provide keratoplasty for patients with corneal disability caused by keratoconus, stromal dystrophy, and stromal scarring. Although excellent results have been obtained with PKP for these indications, an investigation into the suitability and effectiveness of deep anterior lamellar keratoplasty (DALK) is warranted as an alternative to PKP in many of these cases. Employing an alternative to PKP would be of particular benefit to patients with stromal scarring and to older patients with stromal dystrophy, where a high level of vulnerability for graft failure exists after the onset of immune-mediated endothelial rejection episodes—a complication that can be eliminated with DALK. Conversely, the very low level of vulnerability for graft failure after the onset of endothelial rejection episodes in eyes with keratoconus mandates a carefully controlled, prospective clinical trial to determine whether or not differences in visual outcome in eyes treated with DALK offset the elimination of the small risk of rejection-related graft failure before the full conversion from PKP to DALK is justified.

4. Corneal specialists should modify their approach in managing Saudi patients with corneal edema. In response to the documentation of a statistically significant correlation between increasing donor age and the probability of graft survival for this surgical indication, these patients should preferentially be provided with younger, rather than older, donor material. Furthermore, ophthalmologists should begin performing DSAEK

for all patients with phakic corneal edema and for those with pseudophakic corneal edema associated with PC IOLs. Larger donor buttons can be utilized with DSAEK, thereby providing a greater surface area of endothelial replacement and reducing the risks associated with the use of smaller grafts in eyes with compromised recipient peripheral endothelium. Furthermore, DSAEK does not require the placement of corneal sutures, thereby decreasing the risk of microbial keratitis in these eyes with a considerable burden of ocular surface disease, reducing the occurrence of postoperative refractive changes, and increasing the likelihood of successful visual rehabilitation. In carefully selected cases of aphakic corneal edema and pseudophakic corneal edema with AC IOLs, DSAEK can also be utilized when sufficient experience has been gained with this procedure. Irrespective of the method of corneal transplantation, a conservative approach toward offering surgical intervention for corneal edema in patients in KSA is warranted, particularly if the visual acuity is adequate in the contralateral eye for the needs of the patient and the affected eye is relatively comfortable.

VIII. CONCLUSIONS

1. Corneal graft survival and visual outcome for primary adult optical penetrating keratoplasty were not adversely affected by the socioeconomic, cultural, and public health factors present in the Kingdom of Saudi Arabia. Graft survival and visual outcome were less favorable in older patients than younger patients, but these differences were attributed to the prevalence of higher risk indications for keratoplasty and associated ocular comorbidity in older patients, rather than factors related to the ophthalmic care system. The large geographic size of the country and logistical difficulties imposed by travel to a centralized eye care facility, especially for women and older patients, and the necessity of relying almost exclusively on imported corneal donor tissue did not significantly affect surgical outcomes. This success is attributed to the presence of a suitable infrastructure that provides modern eye care facilities, donor tissue, and pharmaceuticals for patients with corneal disabilities who have access to preoperative screening and evaluation, surgical intervention, and postoperative care by well-trained ophthalmologists and ancillary support personnel, as well as assistance from well-organized educational and social services that are essential for promoting patient compliance.

2. Corneal graft survival was excellent for eyes with keratoconus and stromal dystrophy. Among eyes with keratoconus, a previous history of hydrops or the concomitant presence of vernal keratoconjunctivitis did not adversely affect graft survival.

3. Corneal graft survival for eyes with stromal scarring was comparable to that of published Western series. In addition, favorable results were documented for management of well-selected cases of eyes with trachomatous stromal scarring, a condition that is a rare indication for keratoplasty in Western countries, and for which only limited surgical series have previously been published in countries where this condition is endemic. Graft survival was poorer for eyes with corneal edema compared to published Western series. Factors that may have contributed to poorer outcomes in

Saudi patients include a higher prevalence of ocular surface abnormalities, previous glaucoma surgery, and postoperative complications. Patient age, gender, distance from the surgical center, and postoperative visit compliance were not contributing factors.

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X. DISSERTATION PUBLICATIONS

1. Al-Fawaz A, Wagoner MD, and the King Khaled Eye Hospital Cornea Transplant Study Group. Penetrating keratoplasty for trachomatous corneal scarring. Cornea 2008;27:129-132.

2. Wagoner MD, Ba-Abbad R, and the King Khaled Eye Hospital Cornea Transplant Study Group. Penetrating keratoplasty for keratoconus with and without vernal keratoconjunctivitis. Cornea 2008 (in press).

3. Wagoner MD, Ba-Abbad R, Al-Mohaimeed M, Al-Swailem S, Zimmerman MB, and the King Khaled Eye Hospital Cornea Transplant Study Group. Postoperative complications after primary adult optical penetrating keratoplasty: prevalence and impact on graft survival. Cornea (accepted for publication).

4. Wagoner MD, Gonnah ES, Al-Towerki A, and the King Khaled Eye Hospital Cornea Transplant Study Group. Outcome of primary adult penetrating keratoplasty with imported donor corneas. Cornea (accepted for publication).

APPENDIX 1

RESEARCH PROPOSAL

Topic/Scope/Originality/Contribution

To date, factors influencing corneal graft survival and visual outcome have not been systematically studied in a single practice group that is based in a public health setting in a developing country where the citizens rely almost exclusively on a single facility for care and in which fairly consistent surgical techniques and management strategies are employed.

In the Kingdom of Saudi Arabia (KSA), tertiary care eye services, including corneal transplantation, have been centralized in Riyadh at King Khaled Eye Specialist Hospital (KKESH). Patients are provided with sponsored medical and surgical care, free medications, and free airfare (if required) to and from their hospital visits. Adequate budgetary support is provided to enable every suitable candidate to receive a corneal transplant. All patients are treated as inpatients, with similar surgical techniques, postoperative medications, and follow-up schedules.

A retrospective review will be conducted of corneal transplants that were performed during a 5-year period (1997-2001) under these standardized conditions to identify risk factors that significantly affect graft survival. The study will focus on primary grafts performed for optical rehabilitation in patients 12 years of age or older. In addition to quantifying the impact of recipient diagnosis, donor tissue factors, ocular risk factors, surgical parameters, and complications on the prognosis for specific surgical indications for keratoplasty, this study will provide a unique opportunity to assess the importance of local cultural factors (eg, female travel restrictions), socioeconomic factors (eg, prevalence of climatic droplet keratopathy and chronic trachoma), and logistical factors (eg, the distance from a centralized ophthalmic care facility in a geographically large country) on graft survival and visual outcome.

Hypothesis/Anticipated Results

1. Because of socioeconomic, cultural, and public health service (PHS) factors present in KSA, corneal graft survival and visual outcome may be adversely affected, especially in older patients.

2. Corneal graft survival may be similar to that of published Western series for keratoconus and stromal dystrophy because of the predominance of patients younger than 25 and 40 years of age, respectively, for these surgical indications. Specific factors that may have an adverse impact on graft survival in eyes with keratoconus include previous episodes of hydrops and the concomitant presence of vernal keratoconjunctivitis.

3. Corneal graft survival may be less than that of published Western series for stromal scarring (post-trachoma, microbial keratitis, trauma) and corneal edema (phakic, aphakic, pseudophakic), most of which occur in patients older than 50 years of age. Specific factors that may be associated with decreased graft survival include patient age, gender, distance from the surgical center, and postoperative visit compliance.

Background/Pilot Studies

The prognostic determinants of graft outcome after penetrating keratoplasty conducted at a PHS in a developing country are influenced by the following: (1) the availability of facilities and health care providers,[1,2] (2) the availability and quality of donor tissue,[3-7] (3) recipient diagnosis,[8-20] (4) concomitant ocular risk factors,[8-20] (5) postoperative complications,[21-26] and (6) socioeconomic and PHS related risk factors.[16-20,23,24]

Availability of facilities and health care providers. In the second half of the 20th century, KSA utilized the wealth generated by its vast oil reserves to develop and modernize every enterprise in the country, including health care services.[1] The beginning of modern ophthalmology in KSA was marked by the opening of KKESH, which has served as the tertiary care eye facility for the Ministry of Health (MOH) to the present day. On June 1, 1983, corneal transplantation was first performed at KKESH.[2] Currently, the Anterior Segment Division at KKESH consists of 15 full-time, board-certified faculty members who perform over 500 corneal transplants annually. To date, more than 9500 of nearly 12 000 corneal transplants performed in KSA have been done at KKESH.

Availability and quality of donor tissue. Many countries are compromised with respect to their ability to provide corneal transplantation because of a shortage of locally acquired donor tissue. Despite considerable public relations efforts and no religious prohibitions,[1,2] corneal donation in KSA accounts for less than 5% of tissue available for transplantation.[2] Sufficient financial resources permit the acquisition of tissue from foreign eye banks, particularly from the United States.[2] Unfortunately, there is an inevitable delay between donor death and preservation and surgical use of this tissue.[1-3]Although it has been established that the use of tissue that has been preserved for more than 7 days in storage at 4°C prior to surgical utilization is associated with a reduced risk of postoperative endothelial rejection episodes,[4] concerns exist that loss of endothelial cell viability may contribute to a higher incidence of early and late graft failure.[5-7] Fortunately, a review of cases performed at KKESH in 1999 did not demonstrate adverse consequences with respect to either graft survival or visual outcome with the use of donor tissue that had been maintained in Optisol-GS media for more than 7 days. Because the previous series had a relatively limited number of cases and a follow-up period of less than 4 years, it did not completely address the concern of late endothelial failure. The current study will expand this analysis to include all cases performed between January 1, 1997, and December 31, 2001, with an increased length of follow-up (5-10 years) and will either strengthen or refute the pilot study findings.

Recipient diagnosis. One of the most important prognostic factors for corneal transplantation is the surgical indication for which the procedure is performed.[8-20] In Western centers, consistent rates of graft survival have been documented for specific surgical indications, with excellent survival (>90%) in eyes with keratoconus and stromal dystrophies, good survival (50%-90%) in eyes with stromal scarring and corneal edema, and poor survival (<50%) in eyes with acute microbial keratitis or in cases of pediatric keratoplasty.[8-15] Pilot studies performed by the KKESH Cornea Transplant Study Group (CTSG) to evaluate graft survival after penetrating keratoplasty for keratoconus associated with vernal keratoconjunctivitis,[16] macular dystrophy,[17] repeat penetrating keratoplasty,[18] congenital hereditary endothelial dystrophy,[19] and pediatric keratoplasty[20] have also indicated a correlation between surgical indication and graft survival. These studies did indicate, however, some variability with respect to graft survival for the same indication when compared with Western series. For example, increasing patient age[17] and poor compliance with follow-up visits[19] were associated with a statistically increased incidence of graft failure in eyes with macular corneal dystrophy and congenital hereditary endothelial dystrophy, respectively. Both of these findings may be related to logistical problems associated with access to prompt ophthalmic care. The current study will provide an opportunity to assess these risk factors by providing data on graft survival for recipient diagnosis (keratoconus without vernal keratoconjunctivitis; stromal scarring, especially those cases related to trachoma; corneal edema) that have *not* been previously studied by the KKESH CTSG.

Concomitant ocular risk factors. A number of ocular risk factors are inherently associated with an increased risk of graft failure, including increasing patient age, preexisting or new onset glaucoma, previous surgical procedures, and contralateral keratoplasty.[8-15] With the exception of the series on pediatric keratoplasty,[19,20] previous studies by the KKESH CTSG involved relatively young patients with a low incidence of concomitant ocular disorders other than their primary corneal disorder.[17,18]

Most of the patients with stromal scarring and corneal edema in the current study are older than 50 years of age, thereby providing an excellent opportunity to assess the potential adverse effects of a number of ocular risk factors on graft survival.

Postoperative complications. The significant association of major postoperative complications such as immune-mediated endothelial rejection episodes, microbial keratitis, glaucoma escalation, persistent/recurrent epithelial defects, trauma, retinal detachment, and endophthalmitis with decreased graft survival has been well documented in Western studies.[8-15,21-26] In addition, previous studies by the KKESH CTSG have found statistically significant associations between a decreased likelihood of graft survival and endothelial rejection episode,[18,20,25] bacterial keratitis,[16-18,20,26] retinal detachment,[20] and endophthalmitis.[20] These studies suggested that the incidence of bacterial keratitis may be higher for each recipient diagnosis than in comparable Western series[26] and that the incidence of postkeratoplasty infections,[26] as well as their correlation with graft failure,[17] are linearly related to increasing patient age. Hypothetically, the increased incidence of ocular surface disease, as well as logistical

problems related to acute access to the health care system in older patients, may have contributed to these observations. The incidence of major graft complications and their impact on graft survival for all of the recipient diagnoses in the proposed study have *not* been previously performed by the KKESH CTSG. The expanded database in the current study, as well as the longer duration of follow-up, is expected to provide more definitive data about the incidence of postoperative complications in our patient population, as well as differences that may exist with respect to Western centers because of socioeconomic and PHS related factors.

Socioeconomic, cultural, and PHS related risk factors. Because virtually all studies of graft survival have been performed in Western centers, limited data are available with respect to the potential adverse effects of ocular surface disorders such as climatic droplet keratopathy and chronic trachoma on graft survival. As a result of environmental exposure and poor socioeconomic conditions until the middle of the 20th century, climatic droplet keratopathy is almost ubiquitous in Saudi males over the age of 50 years, and sequelae of chronic trachoma are present in most women older than 50 years. To date, the contribution of these risk factors to graft survival has *not* been addressed in studies by the KKESH CTSG. Most of the patients with stromal scarring and corneal edema are older than 50 years of age, thereby providing an excellent opportunity to assess the potential adverse effects of climatic droplet keratopathy and chronic trachoma on graft survival.

Despite access to free care at KKESH, the patient population served by KKESH is scattered over a large geographic area. As a result, logistical problems related to prompt presentation for follow-up care when subjective symptoms occur may be a factor in the timely management of postoperative complications and may adversely affect the prognosis, especially in elderly patients. This is particularly applicable to female patients, who must not only make flight arrangements for impromptu appointments but also arrange to be accompanied by a *mandatory* male travel companion (husband or immediate family member). The recipient diagnosis of cases previously studied by the KKESH CTSG (pediatric keratoplasty,[19,20] keratoconus,[18] macular corneal dystrophy[17]) were biased toward younger patients and did not include enough older patients to address effectively the impact of nuances of the health care system on graft survival. They did, however, provide sufficient evidence of a correlation between patient age and compliance to warrant a more comprehensive evaluation. In the current study, two categories of recipient diagnosis (corneal edema, stromal scarring) consist predominantly of patients older than 50 years of age. An analysis of the outcomes related to these recipient diagnoses is expected to provide an excellent opportunity to evaluate statistically the impact of patient age, gender, distance from the surgical center, and compliance with postoperative visit schedules on graft survival in our patient population and to compare these results with published data from Western centers with advanced public health care systems.

Experimental Design and Methods

A retrospective analysis will be conducted on the patient medical records of all primary optical penetrating keratoplasties performed at KKESH between January 1, 1997, and December 31, 2001, on patients 12 years of age or older for keratoconus, corneal edema, stromal scarring, and stromal dystrophy.

Recipient diagnosis will be further stratified as follows to identify subcategories that may have prognostic significance:

1. *Keratoconus*: with and without vernal keratoconjunctivitis, with and without previous hydrops
2. *Corneal edema*: phakic, aphakic, pseudophakic (anterior chamber, posterior chamber)
3. *Stromal scarring*: secondary to trachoma, post-microbial keratitis (bacterial, fungal), trauma, and other causes
4. *Stromal dystrophy*: macular, granular, lattice

The following variables that potentially influence graft prognosis will be evaluated:

1. *Donor tissue:* donor age, endothelial cell count, death-to-preservation time, preservation-to-surgery time, positive bacterial/fungal cultures
2. *Recipient diagnosis*: keratoconus, corneal edema, stromal scarring, stromal dystrophy
3. *Ocular risk factors:* patient age, preexisting or new onset glaucoma, neovascularization, other surgical procedures, contralateral keratoplasty
4. *Surgical parameters:* donor and recipient trephination size, suture technique, duration of postoperative immunosuppression
5. *Complications:* endothelial rejection episode, microbial keratitis, glaucoma escalation, persistent/recurrent epithelial defects, trauma, retinal detachment, endophthalmitis
6. *Socioeconomic, cultural, and PHS risk factors:* gender, climatic droplet keratopathy, trachoma, distance from surgical center, postoperative visit compliance

The primary outcome measures will be *graft survival* and *visual outcome*. The probability of graft survival will be calculated using Kaplan-Meier survival curves, with the use of 95% confidence intervals at each time point. Graft failure will be defined as irreversible loss of central graft clarity, irrespective of etiology, with loss of best corrected visual acuity (BCVA) to less than 20/40. The time of graft failure will be defined as the first visit at which irreversible loss of central graft clarity is documented. The postoperative visual acuity will be recorded at the most recent follow-up examination or immediately before repeat keratoplasty for unsuccessful grafts. The BCVA will be recorded, if available. If the BCVA is not available, the uncorrected visual acuity will be recorded. In addition, the best recorded visual acuity during the postoperative course will be documented. Outcome measures will be compared with

historical controls of published Western series of corneal transplantation for each recipient diagnosis.

Initially, univariate analysis will be performed to identify significant risk factors. The outcome measures of graft survival will be evaluated using the standard Kaplan-Meier survival analysis. Differences between surgical indication groups and risk factors will be analyzed using Cox proportional hazard ratios. Statistical significance will be defined as 0.05 or less. Factors that are determined to be significant in univariate analysis will be further analyzed with multivariate regression analysis to determine their significance as independent variables. Assistance with statistical analysis will be provided by Dr. M. Bridgett Zimmerman, Department of Biostatistics, College of Medicine, University of Iowa, Iowa City, Iowa, United States.

Ethical Approval

All human study related to this project will consist of a retrospective review of patient medical records at KKESH in Riyadh, Saudi Arabia.

Approval was obtained from the Research Council of KKESH for Research Project 0326-R entitled "Outcome of Penetrating and Lamellar Keratoplasty at KKESH (1993-2002)" on September 22, 2003.

Approval was obtained from the Human Ethics Committee/Institutional Review Board of KKESH for Research Project 0326-R on October 14, 2003.

Approval was obtained from the Ethics Committee for Human Research, Faculty of Health Sciences, University of Stellenbosch for Project Number N06/09/179 entitled "Factors Influencing Graft Survival and Visual Outcome after Penetrating Keratoplasty in a Public Health Service Hospital of a Developing Country," on October 4, 2006.

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APPENDIX 2

DATA COLLECTION SHEET

Recipient Diagnosis

□ Keratoconus
- Vernal keratoconjunctivitis (VKC) □ yes □ no
- Previous hydrops □ yes □ no

□ Corneal scar
- □ Trauma
- □ Post-microbial keratitis
  - □ Bacterial □ Fungal
- □ Trachoma
- □ Other

□ Corneal edema
- □ Aphakic corneal edema
- □ Pseudophakic corneal edema
  - □ Anterior chamber intraocular lens (AC-IOL)
  - □ Iris-plane IOL
  - □ Posterior chamber intraocular lens (PC-IOL)

□ Stromal dystrophy
- □ Macular
- □ Granular
- □ Lattice

Donor Tissue

Age: _____
Death-to-preservation (hours): _____
Preservation-to-surgery (hours): _____
Endothelial cell count (cc/mm^2): _____

Positive bacterial cultures: □ yes □ no
Positive fungal cultures: □ yes □ no

Socioeconomic and PHS Risk Factors

Gender: □ male □ female

Home Province:
□ Central: Najd (Riyadh, Gassim, Kharj)
□ Eastern Province (Damman, Khobar, Dahran, Al-Hasa, Hofuf)
□ Western Province (Jeddah, Taif, Mecca, Medinah)
□ Asir Region (Abha, Baha, Khamees Mushaet)
□ Northern Region (Hail, Arar, Tobuk)

Follow-up (days):
Date of surgery (day/month/year): _____
Date of outcome (day/month/year): _____
If failed graft: date that irreversible failure was first documented
If clear graft: date of most recent examination

Office visits (total scheduled): _____
Office visits missed: _____

Emergency room (ER) visits (total number): _____

Ocular Risk Factors

Age at time of surgery (years): _____

Associated preoperative conditions:

Glaucoma	□ yes	□ no
Neovascularization	□ yes	□ no
Climatic droplet keratopathy	□ yes	□ no
Chronic trachoma	□ yes	□ no
Contralateral keratoplasty:	□ yes	□ no
If yes, graft status (clear, failed)	□ clear	□ failed
Previous surgery	□ yes	□ no
Ruptured globe	□ yes	□ no
Cataract	□ yes	□ no
IOL	□ yes	□ no
Glaucoma	□ yes	□ no
Vitreoretinal	□ yes	□ no

Concomitant surgery	□ yes	□ no
Cataract	□ yes	□ no
IOL	□ yes	□ no
Glaucoma	□ yes	□ no
Vitreoretinal	□ yes	□ no
Subsequent surgery	□ yes	□ no
Ruptured globe	□ yes	□ no
Cataract	□ yes	□ no
IOL	□ yes	□ no
Glaucoma	□ yes	□ no
Vitreoretinal	□ yes	□ no

Surgical Parameters

Donor trephine size (mm): _____

Recipient trephine size (mm): _____

Suture technique:

□ Interrupted only □ Interrupted + continuous □ Continuous only

Corticosteroid duration

- □ Less than 3 months
- □ More than 3 months but less than 6 months
- □ More than 6 months but less than 1 year
- □ More than 1 year

Cyclosporine duration

- □ Not at all
- □ Less than 3 months
- □ More than 3 months but less than 6 months
- □ More than 6 months but less than 1 year
- □ More than 1 year

Complications

□ Microbial keratitis (culture-positive)

- □ Bacterial □ Fungal □ Endophthalmitis

□ Persistent epithelial defect (>14 days)

- □ Immediate postoperative period
- □ After postoperative period

□ Endothelial rejection episode(s)

□ Trauma

- □ Wound dehiscence only
- □ Wound dehiscence with loss of intraocular contents
- □ Wound dehiscence with retinal detachment

□ Glaucoma escalation
    □ Increased medication requirement
    □ Surgical intervention required
□ Retinal detachment

Outcome

Final status

□ clear □ failed

Visual acuity

Best recorded visual acuity after surgery: _____

Final best corrected visual acuity: _____