Long-Term Review of Penetrating Keratoplasty: A 20-Year Review in Asian Eyes

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• PURPOSE: To review the long-term outcomes of optical, therapeutic and tectonic forms of penetrating keratoplasty over a 20-year period in Asian eyes.

• DESIGN: Prospective cohort study involving the Singapore Corneal Transplant Study (SCTS).

• METHODS: All penetrating keratoplasties (PK) performed at the Singapore National Eye Centre (SNEC) from January 1991 to December 2010 were analyzed using records from the computerized database of the SCTS. This database includes preoperative, intraoperative, and postoperative patient data and donor cornea data. Only primary grafts were included. Patient demographics, donor cornea source, indications for grafting, complications, graft survival rate, and causes of graft failure were analyzed.

• RESULTS: A total of 1,206 primary PKs were performed. The mean age of the patients was 55 years (range: <1-101 years). The overall corneal graft survival rates at 1, 5, 10, 15, and 20 years were 91%, 66.8%, 55.4%, 52%, and 44%, respectively. For optical grafts, pseudophakic bullous keratopathy, postinfectious corneal scarring and thinning and keratoconus were the most common diagnoses. Graft survival for optical grafts was significantly better than therapeutic and tectonic grafts at all time points. Multivariate analysis suggested that a younger donor cornea age and higher donor endothelial cell count are associated with better long-term graft survival for optical grafts. Irreversible allograft rejection and late endothelial failure accounted for more than 60% of graft failures.

• CONCLUSIONS: Graft survival decreased over time from 91% at 1 year to 44% at 20 years' follow-up. Allograft rejection and late endothelial failure accounted for more than 60% of graft failures. (Am J Ophthalmol 2021;224:254–266. © 2020 Elsevier Inc. All rights reserved.)

THERE IS CUMULATIVE EVIDENCE TO SUGGEST THAT outcomes of solid organ transplants have improved steadily over time in recent years.[1–3] Increasing efficacy of systemic immunosuppression and effective histocompatibility matching has been attributed to the improvements seen in survival rates for solid organ transplants. Assuming that cornea is immune-privileged, it was thought that survival outcomes of corneal transplants would be better than solid organ grafts; however, in a large series reported by Coster and associates[4] from the Australian Corneal Graft registry, corneal graft survival has not improved with time. In their series of 10,952 penetrating keratoplasty (PK) procedures, graft survival rate was reported to be 86% at 1 year and 55% at 15 years postoperatively. They also compared graft survival for PKs performed within 3-4 year blocks from 1985 to 2003 and showed that there was no improvement in survival with era. Allograft rejection was cited as a cause for graft failure in nearly one-third of cases. A similar outcome was also reported by Borderie and associates,[5] where the overall observed midterm graft survival rate was 74% at 5 years and 64% at 10 years, and the predicted long-term graft survival rate was 48% at 15 years, 27% at 20 years, and 2% at 30 years. In fact, corneal graft survival also seems worse than patient survival after renal transplantation, which has been reported to be in the range of 60% to 65% at 15 years after surgery.[2]

The Singapore Corneal Transplant Study (SCTS) is a corneal transplant registry in Singapore, established since 1991, which is unique in prospectively tracking outcomes of all forms of penetrating and lamellar keratoplasties in an Asian setting with substantially different disease indications compared to Western populations.[6,7] Risk factors for graft failure in that study were reviewed, as were long-term graft outcomes of optical, therapeutic, and tectonic forms of penetrating keratoplasty over a 20-year period.

MATERIALS AND METHODS

WE ANALYZED ALL PKS PERFORMED AT THE SINGAPORE NAtional Eye Centre (SNEC) between January 1991 and

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December 2010 using records from the computerized database of the prospective SCTS.[6] This database includes preoperative, intraoperative and postoperative patient data as well as donor cornea data recorded on a yearly basis since 1991.

For purposes of the current study, only primary grafts performed for optical, tectonic, and therapeutic indications were included. The following exclusion criteria were: lamellar keratoplasties and secondary or subsequent PKs. All penetrating grafts retrieved from the database were divided into 4 subgroups depending on the date of grafting in blocks of 5-year intervals: 1991-1995, 1996-2000, 2001-2005, and 2006-2010. Then the following variables were compared among the 4 subgroups: patient demographics (age, sex, and race), donor cornea sources (local vs. foreign), indications for grafting, visual outcomes, complications, graft survival rate, and causes of graft failure. Additionally, the overall graft survival over a period of 20 years was also analyzed for all indications as well as those based on primary diagnosis.

Approval was obtained for this study from the Singapore Eye Research Institute institutional review board (2011/577/A). Because this study was a retrospective review of de-identified data, a waiver of informed consent was granted.

• **STATISTICAL ANALYSIS:** The survival rates of corneal grafts were determined using the Kaplan-Meier method. Graft failure was defined as the irreversible loss of optical clarity, with the date of onset of corneal clouding selected as the time point of graft failure. For documented failed grafts, the survival period of the graft was defined as the interval between the date of surgery and the date of failure. For the censored surviving grafts and cases lost to follow-up, the survival period was calculated as the interval between the date of surgery and the date of the last visit. The Mantel-Cox log rank test was used to compare survival curves.

A univariate Cox regression test was conducted to examine donor cornea-specific risk factors, and a multivariate cox regression was conducted from significant findings and consideration for multicollinearity. A P value of $<.05$ was considered statistically significant. All analyses were processed using SPSS version 24.0 software (IBM, Armonk, New York, USA) for Windows (Microsoft, Redmond, Washington, USA).

RESULTS

BETWEEN 1991 AND 2010, 1,206 PRIMARY PKS WERE performed at SNEC. The number of PKs performed between 1996 and 2000 and 2001 and 2005 was stable, whereas a reduction in the number of PKs was noted between 2006 and 2010, and this was in keeping with the increase in lamellar graft surgery at the authors' center during a similar time frame.

TABLE 1. Patient Demographics and Cornea Donor Source

Age	1991-2010 n	%
Age <16	32	2.7
16 ≤ age <40	259	21.5
40 ≤ age <60	314	26.0
60 ≤ age <80	521	43.2
Age ≥80	80	6.6
Total	1206	100.0
Sex	n	%
Male	693	57.5
Female	513	42.5
Total	1206	100.0
Race	n	
Chinese	841	69.7
Malay	139	11.5
Indian	105	8.7
Others	121	10.0
Total	1206	100.0

Cornea Donor Source	1991-1995		1996-2000		2001-2005		2006-2010	
	n	%	n	%	n	%	n	%
Local	61	24.5	144	41.5	104	30.2	109	41.0
Foreign	188	75.5	203	58.5	240	69.8	157	59.0
Total	249	100.0	347	100.0	344	100.0	266	100.0

Follow-Up Period (Duration from Last Visit Date to Operation Date)

	Overall	Optical Cases	Tectonic Cases	Therapeutic Cases
Range	3 d-23 y[a]	3 d-23 y[a]	5 d-17 y[a]	4 d-14 y[a]
Mean	4.7 y	5 y	2.5 y	2.4 y
Median	3 y	3.2 y	1.1 y	1 y

[a]Most patients who were followed less than 1 year were overseas patients.

• **PATIENTS' AND CORNEA DONORS' DEMOGRAPHICS:** Mean age was 55 years (range: <1-101 years). An increasing number of pediatric cases were treated between 2006 and 2010. Generally, a greater number of male patients (57.5%) underwent PK than females (42.5%), and this was consistent over time. Overall follow-up period ranged from 3 days to 23 years (mean: 4.7 years; median: 3 years) (Table 1).

As shown in Table 1, more than half of the donor corneas used for transplantation were obtained from eye banks outside Singapore; 30-40% of donor corneas were procured from the Singapore Eye Bank.

• **ENDOTHELIAL CELL COUNT DATA:** Donor corneas obtained from the Sri Lanka Eye Bank from 1991 to 1999 did not have endothelial cell count (ECC) information. Donor corneas from the United States had ECC data from

TABLE 2. Diagnosis by Different Surgical Indications

	Optical		Tectonic		Therapeutic	
Diagnosis	n	%	n	%	n	%
PBK	280	26.7	1	1.5	0	0.0
Post-infectious scar/thinning	140	13.3	4	5.9	0	0.0
Anterior keratoconus	121	11.5	0	0.0	0	0.0
Corneal injury	100	9.5	9	13.2	2	2.3
FED	95	9.0	0	0.0	0	0.0
Aphakic bullous keratopathy	87	8.3	0	0.0	0	0.0
Other corneal dystrophy	59	5.6	1	1.5	0	0.0
Non-traumatic/non-infectious corneal scar	36	3.4	2	2.9	2	2.3
Non-traumatic/non-surgical corneal edema	34	3.2	0	0.0	1	1.1
Glaucoma	34	3.2	0	0.0	0	0.0
Post-laser PI corneal decompensation	16	1.5	0	0.0	0	0.0
Non-infectious ulcer/degeneration	13	1.2	9	13.2	1	1.1
Congenital	12	1.1	1	1.5	0	0.0
Uveitis	7	0.7	0	0.0	1	1.1
Post herpetic scar/degeneration	2	0.2	0	0.0	0	0.0
Non-infectious corneal melt/perforation	1	0.1	18	26.5	1	1.1
Infectious keratitis	0	0.0	20	29.4	77	87.5
Others	13	1.2	3	4.4	3	3.4
Total	1050	100	68	100	88	100

High-Risk Proportion for PBK and FED (Optical Cases Only)

	Diagnosis				
High Risk[a]	PBK		Non-PBK		P Value
Yes	109	38.9%	220	28.6%	.001
No	171	61.1%	550	71.4%	
Total	280	100%	770	100%	

	Diagnosis				
High Risk[a]	FED		Non-FED		P Value
Yes	13	13.7%	316	33.1%	<.001
No	82	86.3%	639	66.9%	
Total	95	100%	955	100%	

FED = Fuchs' endothelial dystrophy; PBK = pseudophakic bullous keratopathy; PI = peripheral iridotomy.

$\chi 2$ test was used to obtain the *P* values.

[a]High-risk factors included deep vascularization with more than 1 quadrant, glaucoma, active inflammation, ocular surface disease, and anterior synechiae.

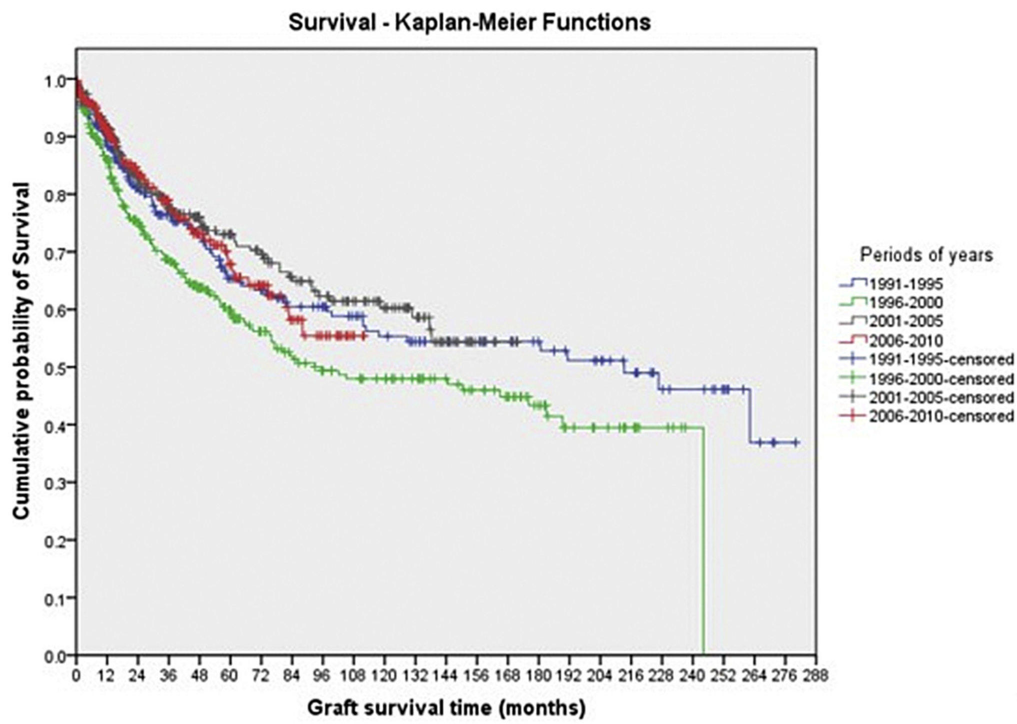
TABLE 3. Postoperative Complications for All Indications at Any Time Point.

	Optical		Tectonic		Therapeutic	
Complications	n	%	n	%	n	%
Glaucoma/raised IOP	247	23.5	14	20.6	12	13.6
Allograft rejection	178	17.0	4	5.9	12	13.6
Late endothelial failure	140	13.3	5	7.4	3	3.4
Epithelial problems	130	12.4	13	19.1	24	27.3
Cataract formation	37	3.5	4	5.9	7	8.0
Wound dehiscence	30	2.9	0	0.0	1	1.1
Microbial keratitis	23	2.2	6	8.8	11	12.5
Post-op anterior synechiae at graft host junction	17	1.6	1	1.5	1	1.1
Primary graft failure	16	1.5	1	1.5	4	4.5
Activation of HSV	13	1.2	1	1.5	1	1.1
Recurrence of primary disease	9	0.9	2	2.9	8	9.1
Endophthalmitis	4	0.4	1	1.5	2	2.3
Suture abscess	0	0.0	0	0.0	1	1.1
Others	161	15.3	9	13.2	19	21.6
Total	1,050	100	68	100	88	100

HSV = herpes simplex virus; IOP = intraocular pressure; Post-op = post-operative.

1996 onward and were obtained mainly from the Central Florida Eye Bank (now Lion's Eye Institute for Transplant and Research). For the US donor corneas from 1996 to 1998, only the endothelial cell density (ECD) value was provided. From 2000 to 2010, specular image and ECD were obtained through the fixed frame-center method using the KSS 300 eye bank specular microscope (Konan, Irvine, California, USA). Donor corneas were obtained from St. Lucia International Eye Bank (Manila, Philippines) from 2007 to 2010. From 2007 to 2008, only the ECD value was available. From 2009 to 2010, a specular image and the ECD were recorded using the EKA-98 specular microscope with fixed frame-center method of counting (Konan). For the Singapore Eye Bank donor corneas, no ECC information was available from 1991 to 1995. From 1996 to 1999, only the ECD value was provided for the donor cornea evaluation forms using an EB-1 specular microscope attached to a video microscope system (Alcon, Geneva, Switzerland). From 2000 to 2010, ECD values were provided with the EKA-98 specular microscope using the fixed-frame analysis center method (Konan). A specular image was printed together with the ECD value and other parameters, checking for cell size, polymorphism, and polymegathism.

• **DIAGNOSIS:** Table 2 shows the diagnosis at the time of the first PK for all 3 indications. For optical grafts, pseudophakic bullous keratopathy (PBK), postinfectious corneal scarring and thinning, keratoconus, corneal injury, and Fuchs' endothelial dystrophy (FED) were the most common diagnoses. Of the PBK grafts, 38.9% were high-risk grafts, and this percentage was significantly higher than that for non-PBK high-risk grafts (28.6%; $P = .001$). Of the FED grafts, 13.7% were high-risk grafts, and this percentage was significantly lower than that of non-FED



Survival time	Year 1991-1995		Year 1996-2000		Year2001-2005		Year 2006-2010	
	Number Entering	Survival Rate	Number Entering	Survival Rate	Number Entering	Survival Rate	Number Entering	Survival Rate
1st year	249	88.3%	347	86.0%	344	91.5%	266	91.3%
2nd year	197	81.1%	256	75.1%	273	83.0%	178	83.3%
3rd year	159	76.4%	203	68.7%	195	77.6%	122	78.9%
4th year	138	72.3%	174	63.8%	160	76.0%	99	73.1%
5th year	120	65.4%	142	59.9%	131	73.0%	78	67.8%
10th year	70	55.3%	68	48.0%	61	60.3%	-	-

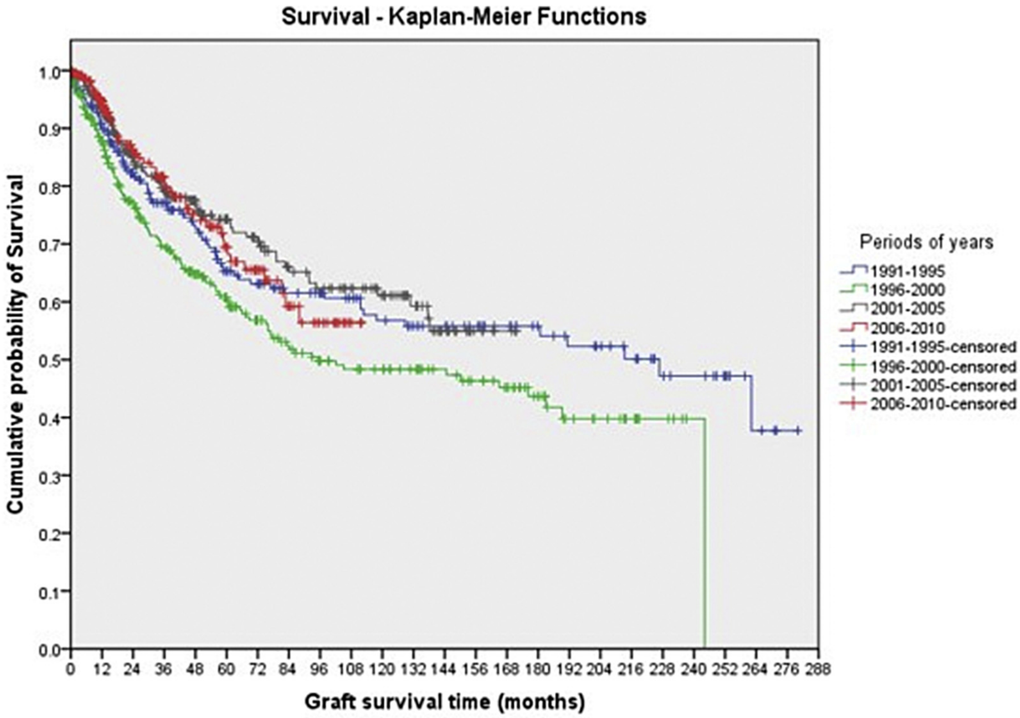
1996-2000 vs.1991-1995: p = 0.032.
1996-2000 vs.2001-2005: p = 0.003.
1996-2000 vs.2006-2010: p = 0.039.
No significant difference for other survival curves comparisons.
Log Rank test was conducted for p values. P=0.05 is considered as significance level.

FIGURE 1. Survival curves for PK for all indications by every 5-year period from 1991 to 2010. PK = penetrating keratoplasty.

high-risk grafts (33.1%; $P < .001$). High-risk factors included deep vascularization with more than 1 quadrant, glaucoma, active inflammation, ocular surface disease, and anterior synechiae.

• **COMPLICATIONS:** Table 3 shows the major complications that occurred at any time during follow-up for all indications. For optical grafts, glaucoma, rejection, and late endothelial failure accounted for more than one-half of the complications seen postoperatively. For tectonic and therapeutic grafts, glaucoma and epithelial problems were the major complications encountered.

• **GRAFT SURVIVAL RATE:** The overall corneal graft survival rates at 1, 5, 10, 15, and 20 years were 91%, 66.8%, 55.4%, 52%, and 44%, respectively. The overall graft survival rates for all indications in 5-year blocks between 1991 and 2010 are shown in Figure 1 and for optical grafts alone are shown in Figure 2. Graft survival was significantly better between 1996 and 2000 versus 1991 and 1995 ($P =$



Survival time	Year 1991-1995		Year 1996-2000		Year2001-2005		Year 2006-2010	
	Number Entering	Survival Rate	Number Entering	Survival Rate	Number Entering	Survival Rate	Number Entering	Survival Rate
1st year	227	89.9%	299	87.8%	297	93.7%	227	94.6%
2nd year	186	82.2%	228	77.0%	247	85.1%	162	85.6%
3rd year	149	77.1%	184	69.7%	182	79.2%	113	81.6%
4th year	129	72.7%	160	64.8%	151	77.6%	92	75.1%
5th year	112	65.3%	135	60.7%	122	74.3%	73	69.4%
10th year	66	56.8%	66	48.3%	57	61.1%	-	-

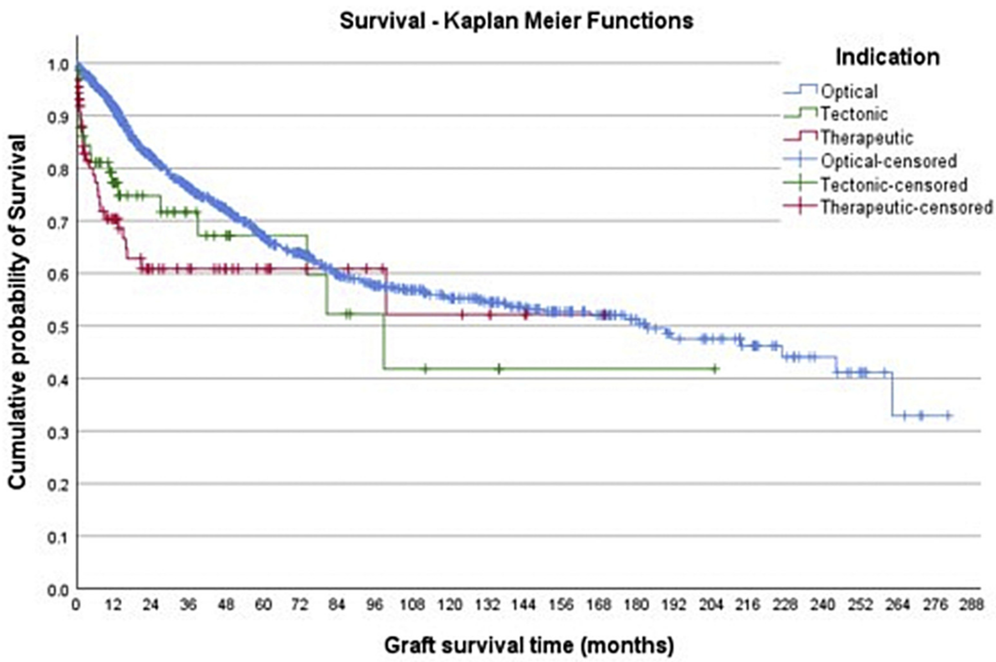
1996-2000 vs.1991-1995: p = 0.034.
1996-2000 vs.2001-2005: p = 0.004.
1996-2000 vs.2006-2010: p = 0.026.
No significant difference for other survival curves comparisons.
Log Rank test was conducted for p values. P=0.05 is considered as significance level.

FIGURE 2. Survival curves for optical PK by every 5-year period from 1991 to 2010. PK = penetrating keratoplasty.

.032 for all PKs; $P = .034$ for optical PKs); between 1996 and 2000 versus 2001 and 2005, respectively ($P = .003$ for all PKs and $P = .004$ for optical PKs), as well as between 1996 and 2000 versus 2006 and 2010, respectively ($P = .039$ for all PKs and $P = .026$ for optical PKs).

Graft survival for optical grafts was also significantly better than therapeutic and tectonic grafts at all time points (Figure 3). No differences in survival rates were seen between therapeutic and tectonic grafts. In addition, survival for optical grafts was significantly better for local donor cornea sources than for donor corneas obtained from overseas (Figure 4) (Table 4).

Graft survival according to preoperative diagnosis is illustrated in Graft 5. The graft survival rates for PBK cases at 1, 5, 10, and 15 years were 89.8%, 47.2%, 34.7%, and 33.0%, respectively. Survival rates for FED cases at 1, 5, 10, and 15 years were 95.7%, 74.9%, 55.3%, and 42.7%, respectively; and rates for keratoconus cases at 1, 5, 10, 15, and 20 years were 99.2%, 99.2%, 97.4%, 94.7%, and 94.7%, respectively.



Survival time	Optical		Tectonic		Therapeutic	
	Number Entering	Survival Rate	Number Entering	Survival Rate	Number Entering	Survival Rate
1st year	1050	91.4%	68	77.3%	88	70.4%
5th year	442	67.1%	12	67.2%	17	60.9%
10th year	193	55.3%	4	41.8%	6	52.2%
15th year	79	51.3%	1	41.8%	1	52.2%
20th year	21	44.1%	-	-	-	-

Optical vs. Tectonic: p = 0.025
Optical vs. Therapeutic: p = 0.001
Tectonic vs. Therapeutic: p = 0.581
Log Rank test was conducted for p values.

FIGURE 3. Survival curves for PK by different indications. PK = penetrating keratoplasty.

The estimated marginal means for graft survival was 189 months (95% confidence interval [CI]: 174-203), 136 months (95% CI: 123-149), 64 months (95% CI: 51-77), and 141 months (95% CI: 117-165) for donors sourced from Singapore, the United States, Manila and Sri Lanka respectively (log rank *P* value = .003 overall). Pairwise comparisons showed that locally sourced corneas from Singapore vs. corneas imported from the United States (p=0.001), and locally sourced corneas Singapore vs. imported from Sri Lanka (p=0.006) was statistically significant.

Table 4 shows the cumulative probability of graft survival at 10 years for local donor corneas was 66.3% (95% CI: 60.1-71.9) and 51.2% (95% CI: 44.3-58.1), respectively, for US donor corneas and 51.2% (95% CI: 39.6-62.8) for Sri Lankan donor corneas. (Note: the short follow-up for Manila donor corneas was 83 months). Cumulative probability of graft survival at 20 years was 57.4% (45.3-69.6 years) for local donor corneas and 36.4% (16.2-56.2) for Sri Lankan donor corneas. (Note: follow-up for US donor corneas was 236 months).

A univariate Cox regression was conducted to examine donor-specific factors such as donor source, donor age, donor sex, donor ECC, donor size, death to operation time in days, and donor race. A multivariate cox regression was conducted from significant findings and consideration for multicollinearity. In univariate analyses, donor source, donor age, donor ECC, donor size, and recipient size were statistically significant ($P < .05$). For donor cornea source, pairwise

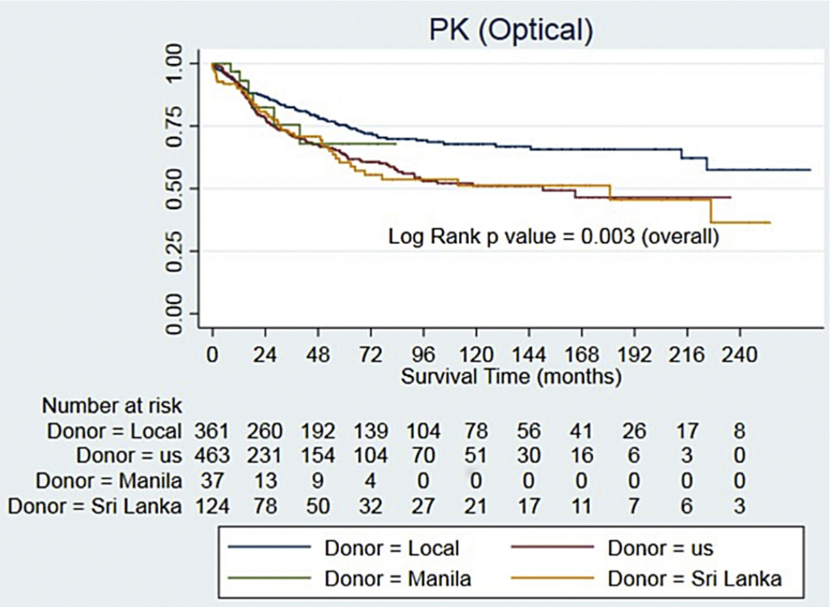


FIGURE 4. Survival curves for PK by donor source (local, United States, Manila, and Sri Lanka); n = 985, failure event = 280, and censored = 750. PK = penetrating keratoplasty.

comparison of US donors in reference to local donors showed a hazard ratio (HR) of 1.56 (95% CI: 1.2-2.1; $P = .001$) and Sri Lankan donor corneas in reference to local corneas showed an HR of 1.16 (95% CI: 1.15-2.3; $P = .007$). For donor cornea age, a per-unit increase in donor age showed an HR of 1.01 (95% CI: 1.0-1.02; $P = .001$). For donor cornea size, a per-unit increase in donor size showed a HR of 0.64 (95% CI: .46-.89; $P = .007$). For recipient size, a per-unit increase in recipient size showed an HR of 0.78 (95% CI: .65-.93; $P = .007$). Donor sex, death to operation time in days, and donor race were not statistically significant (Table 5)

A multivariate cox regression was analyzed using significant univariate factors such as donor cornea source, donor age, donor ECC, and donor size. Recipient size was due to multicollinearity, and a separate model in substitution with recipient size for donor size did not improve model fit. The multivariate cox regression showed that the effect of donor source was no longer statistically significant among the groups (note: Sri Lanka donor corneas lacked ECC data). Only donor age and donor ECC remained statistically significant. For donor age, a per-unit increase in donor age showed an HR of 1.01 (95% CI: 1.0-1.03; $P = .040$). Similarly, for donor ECC, a per-unit increase in donor ECC showed an HR of 0.9991 (95% CI: .99996-.99996; $P = .032$) (Table 6).

• **CAUSES OF GRAFT FAILURE:** Irreversible allograft rejection and late endothelial failure accounted for more than 60% of graft failures in all 4 subgroups (Table 7). Table 8 illustrates the number of grafts with glaucoma: 17.3% of cases with pre-existing glaucoma and 22.7% of cases with postoperative glaucoma. Of these, pre-existing glaucoma was significantly associated with graft failure ($P < .001$), whereas postoperative glaucoma was not ($P = .359$)

DISCUSSION

A FUNCTIONALLY CLEAR GRAFT IS RECOGNIZED AS AN important metric for evaluating transplantation success, and the present study shows that penetrating graft transplantations performed for optical indications survived significantly better than therapeutic and tectonic grafts. It is a well-established fact that therapeutic and tectonic grafts are high-risk grafts and have poorer long-term survival, given erosion of immune privilege by corneal neovascularization, active infection, and inflammation. More importantly, results of this study show that graft survival for optical indications improved with the era.

Although a steady increase has been observed in the number of corneal transplants performed in SNEC on a yearly basis, there has been a reduced trend in the number of PKs over time. This is because of a shift toward lamellar corneal grafts at the authors' center, with PK being generally reserved for high-risk cases that are not amenable to lamellar graft surgery. Despite this shifting trend, optical PKs performed better with time, and a subanalysis revealed that this was likely due to improvement in donor cornea quality over time. Results of the current study contrast sharply to those in reports by the Australian Corneal Graft Registry (ACGR), which found no improvement in graft survival with the era.[4] However, the ACGR analyzed graft survival over all for all indications (eg, optical, therapeutic,

TABLE 4. Cumulative Survival Percentages for Corneal Donor Groups

Donor n, n Corneas	M24 % (95% CI)	M48 % (95% CI)	M72 % (95% CI)	M96 % (95% CI)	M120 % (95% CI)	M144 % (95% CI)	M168 % (95% CI)	M192 % (95% CI)	M216 % (95% CI)	M240 % (95% CI)
Local	86.5%	78.3%	72.1%	69.2%	66.3%	65.7%	65.7%	65.7%	62.2%	57.4%
361	(82.8-90.2)	(73.6-83.0)	(66.6-77.6)	(63.5-74.9)	(60.1-71.9)	(60.0-72.6)	(60.0-72.6)	(60.0-72.6)	(53.7-71.2)	(45.3-69.6)
US	78.3%	67.7%	60.8%	53%	51.2%	49.3%	46.5%	46.5%	46.5%	
463	(73.9-82.6)	(62.6-72.8)	(54.9-66.7)	(46.3-59.7)	(44.5-57.9)	(41.7-56.9)	(37.7-55.3)	(37.7-55.3)	(37.7-55.3)	
Manila	82.5%	68%								
37	(66.2-98.7)	(45.5-90.5)								
Sri Lanka	80.9%	70.8%	55.5%	53.7%	51.2%	51.2%	51.2%	45.6%	45.6%	36.4%
124	(73.6-88.1)	(61.9-79.6)	(44.3-66.7)	(42.5-64.9)	(39.6-62.8)	(39.6-62.8)	(39.6-62.8)	(30.9-60.2)	(30.9-60.2)	(16.2-56.2)

M = month.

and tectonic grafts), so the results of the present study cannot be directly extrapolated to the findings of the ACGR.

For this Asian cohort, indications for PKs were different from those of an American cohort in the Corneal Donor Study (CDS). Notably in the Asian cohort in this study, Fuchs dystrophy represented 9% of cases versus 62% of cases in the CDS.[8] In addition, in this Asian cohort, postinfectious scar and keratoconus constituted 13.3% and 11.5%, respectively, whereas there were no keratoconus or cornea scar cases in the CDS. The shift toward lamellar surgery in the authors' center occurred after 2006, hence, the period of 1991-2006 included keratoconus cases for penetrating keratoplasty.

Over time, more local donor corneas from younger age groups and better ECC were made available. In 1996, the Hospital Eye Donation Program was initiated in Singapore to boost local donor rates. This development involved actively counseling the next of kin of deceased patients regarding the possibility of corneal donation. Within 1 year, the present local donor cornea rates increased by 240%. Our results showed that the era 1996-2000 had the highest local donor cornea rates at 41.5% (Table 1). In 2004, another law came into effect: the Human Organ Transplant Act (HOTA). Prior to this act, Singapore used an opt-in system, where relatives had to decide on whether the corneas could be recovered from the deceased patient if he or she had not left an expressed consent. With the HOTA law, the system was changed to an opt-out system, where all deceased patients were considered donors if the contrary had not been expressly indicated during life. Currently, 40% of donor corneas are procured locally. For optical grafts, a pairwise comparison showed that donor corneas from local sources fared significantly better than those from the United States ($P = .001$) or Sri Lanka ($P = .006$) (Table 4, Figure 4). However, the multivariate cox regression showed that the effect of the donor source was no longer statistically significant among the groups and only donor age and donor ECC remained statistically significant (Table 6). Present results suggest that a higher donor ECC is associated with better long-term graft survival, and these findings are similar to those reported by Nishimura and associates,[9] who showed that 21 graft failures caused by endothelial decompensation had a lower preoperative donor ECD than 367 cases that did not fail (mean: 2710 cells/mm^2 vs. 2991 cells/mm^2, respectively). This is in contrast to the CDS which showed that preoperative ECD was not predictive of graft failure caused by endothelial decompensation at 5[10] and 10[11] years of follow-up.

The present results also suggest that a younger donor age is associated with better long-term graft survival, and this is similar to the findings of the CDS research group who evaluated the effect of donor age on graft survival after 10 years in PKs for endothelial disease such as Fuchs' dystrophy or pseudophakic corneal edema.[8] Although the primary analysis in this report did not show significant differences in 10-year success rates comparing donor ages 12-65 and 66-75, there was evidence of a donor age effect at the extremes of the age range. When donor age was analyzed as a continuous variable, using the exact donor age in the analysis, higher donor age was associated with lower graft success after the first 5 years ($P < .001$). Results were similar after adjusting for baseline ECD. Inspection of the data suggested inflection points for differences in success rates at a donor age of 33 years, below which the 10-year success rate was higher, and at a donor age of 72 years, above which the 10-year success rate was lower. The lower success rate with corneas from donors 72-75 years of age relative to the younger donor ages was not apparent until after 6 years of follow-up.

The 2015 report by the CDS group showed that donor age was not a factor in survival of most PKs for endothelial disease, other than the previously reported suggestion of an association between the extremes of donor age and graft outcome. Secondary analyses confirmed the importance of surgical indication and presence of glaucoma in outcomes at 10 years.[11] Of the preoperative risk factors,

TABLE 5. Univariate Cox Regression on Donor Variables

Cox Regression (Breslow Method for Ties)					
Univariate					
Predictors	n	HR	P>|z|	95% CI	
Donor				Lower	Upper
Local	361	ref = 1			
United States	463	1.56	**.001**[a]	1.23	2.09
Manila	37	1.16	**.719**[a]	0.51	2.67
Sri Lanka	124	1.64	**.007**[a]	1.15	2.34
Univariate					
Males	665	ref = 1			
Female	377	1.05	.663	0.83	1.33
Univariate					
Donor age	1,036	1.01	**.001**[a]	1.00	1.02
Univariate					
Donor ECC	768	0.999	**<.001**[a]	0.999	0.9996
Univariate					
Opdonorsize	1026	0.64	**.007**[a]	0.46	0.89
Univariate					
Oprecipsize	1037	0.78	**.007**[a]	0.65	0.93
Univariate					
DeathtoOp	1040	1.01	.252	1.00	1.01
Univariate					
Donor race (Chinese)	301	ref = 1			
Malay	6	2.00	.239	0.63	6.33
Indian	31	0.84	.684	0.37	1.93
White	475	1.42	**.012**[a]	1.08	1.87
Others	220	1.39	**.046**[a]	1.01	1.92

CI = confidence interval; DeathtoOp = death to operation time; ECC = endothelial cell count; HR = hazard ratio; Opdonorsize = corneal donor diameter; Oprecipsize = recipient trephination diameter.

[a]*P* values in boldface are statistically significant.

TABLE 6. Multivariate Cox Regression on Donor Variables

Predictors	n	HR	P>|z|	95% CI	
Donor				Lower	Upper
Local	277	ref = 1			
United States	427	1.21	.291	0.84881	1.72748
Manila	37	1.87	.176	0.75483	4.63402
Donor age	741	1.0137	**.04**	1.00064	1.02699
Donor ECC	741	0.9995	**.032**	0.99906	0.99996
Donor size	741	0.95	**.774**	0.64271	1.39000

CI = confidence interval; ECC = endothelial cell count; PK = penetrating keratoplasty.

P values in boldface are statistically significant. PK optical n = 741 and failure events = 195. Cox regression = Breslow method for ties.

recipient diagnosis was the most important predictor of outcome, with pseudophakic corneal edema grafts failing at almost twice the rate of grafts for Fuchs' dystrophy. Preoperative glaucoma, especially prior surgical glaucoma treatment, was associated with early failure. Glaucoma surgery, particularly tube drainage devices, has been strongly associated with graft failure.[11]

Hence, in this report, although graph survival data show statistically significant differences between donor sources and between year cohorts, multivariate analysis showed that only 2 factors affected graft survival: donor age and ECC, and not donor source. This means that, although there are statistical differences in graft survival between sources and year of cohorts, the reason is more likely to be differences in donor age and ECC. Therefore, local donor sources have better survival due to younger donors and better ECCs as a consequence. Also, for the cohort years, the improvement of PK success over time is also due to the increase in local donors (hence younger donors with higher ECC) over time (Table 1).

The overall rates of corneal graft survival at 1, 5, 10, 15, and 20 years of 91%, 66.8%, 55.4%, 52%, and 44%, respectively, were lower than those reported by the CDS group of 21% failure rate at 10 years' follow-up.

The next section discusses the possible reasons for the differences in survival rate between the 2 studies.

The current report showed that, similar to previous studies,[4] keratoconus grafts had the best survival outcome of all recipient diagnoses (99.2%, 99.2%, 97.4%, 94.7%, and 94.7% at 1, 5, 10, 15, and 20 years, respectively). PBK grafts failed significantly more than Fuchs' dystrophy grafts (34.7% versus 55.3%, respectively; survival at 10 years) (Figure 5). This finding is similar to that in the 2015 report by the CDS group, which showed that at 10 years' follow-up, FED grafts had a lower failure rate of 20% than pseudophakic/aphakic corneal edema cases with a higher failure rate of 37%.[11] However, the PBK grafts in the present study had a lower survival rate of 34.7% at 10 years compared with that of the Cornea Donor Study group failure rate of 37%. This could be due to the small sample size (23 cases at 10 years' follow-up) and the fact that there were more high-risk grafts among PBK grafts (38.9%) than with non-PBK grafts of 28.6% (P = .001) (Table 2). At 10 years' follow-up, the FED grafts in the present study also had a lower survival rate of 55.3% compared with that of the CDS group of 20% failure rate. This could be due to small sample size of 20 grafts at 10 years follow-up and the fact that during the period 1991-2010, several of the FED cases may have actually been due to undiagnosed cytomegalovirus endotheliitis. Hence, when recurrence of cytomegalovirus infection occurred in the graft, it was mistaken for allograft rejection and inappropriate treatment instituted leading to graft failure. Cytomegalovirus endotheliitis leading to corneal decompensation was recognized as a disease entity only within the past 10 years.[12]

TABLE 7. Cause for Graft Failure Between 1991 and 2010 in 5-Year Blocks

	1991-1995		1996-2000		2001-2005		2006-2010	
Major Causes of Failures	n	%	n	%	n	%	n	%
Rejection	30	37.5	40	33.9	25	35.2	15	41.7
Endothelial failure	31	38.8	34	28.8	26	36.6	14	38.9
Glaucoma	9	11.3	17	14.4	10	14.1	4	11.1
Infection	3	3.8	6	5.1	3	4.2	5	13.9
Epitheliopathy	5	6.3	12	10.2	4	5.6	2	5.6
Recurrence of primary disease	2	2.5	1	0.8	2	2.8	0	0.0
Other	5	6.3	20	16.9	8	11.3	3	8.3
Total number of failures	80	100	118	100	71	100	36	100

TABLE 8. Relationship Between Glaucoma and Graft Failure

Cases With Pre-Operative Glaucoma and Post-Operative Glaucoma	n	%
Pre-op glaucoma	209	17.3
Post-op glaucoma	274	22.7
Total grafts	1,206	

Relationship Between Glaucoma and Failure/Rejection

	Glaucoma[a]				
Failed/Rejected	Yes %		No %		*P* Value
Yes	182	43.9	278	35.1	.003
No	233	56.1	513	64.9	
Total	415	100	791	100	

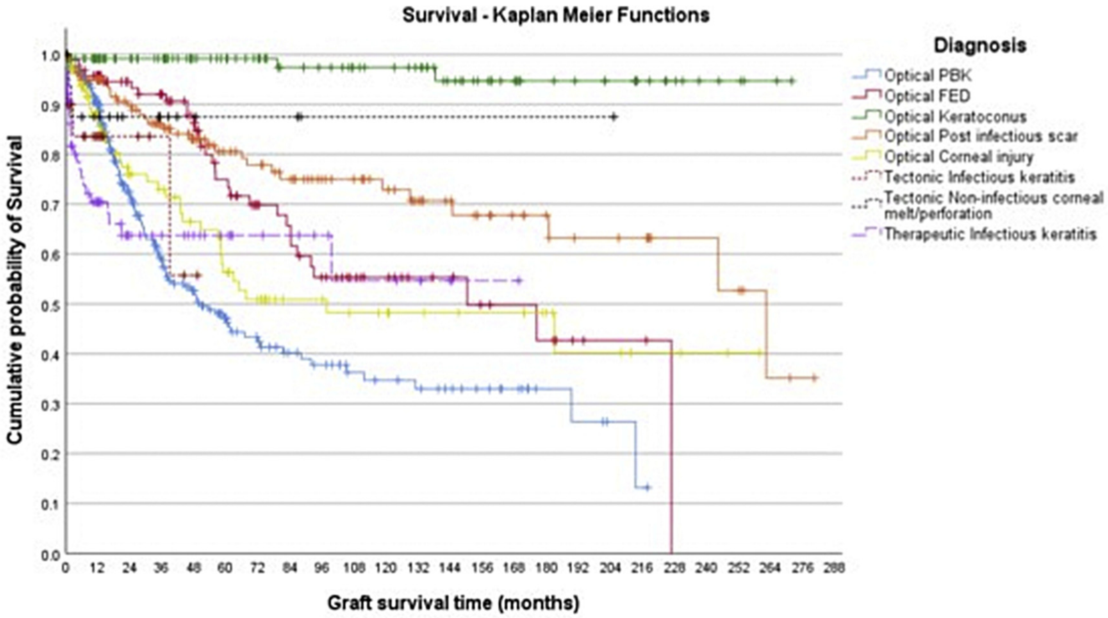
	Pre-Existing Glaucoma				
Failed/Rejected	Yes %		No %		*P* Value
Yes	111	53.1	349	35.0	<.001
No	98	46.9	648	65.0	
Total	209	100	997	100	

	Post-Op Glaucoma				
Failed/Rejected	Yes %		No %		*P* Value
Yes	111	40.5	349	37.4	.359
No	163	59.5	583	62.6	
Total	274	100	932	100	

Pre-op = pre-operative; Post-op = post-operative.
χ^2 test was used to obtain the *P* value.
[a]Including pre-op existing glaucoma and post-operative glaucoma complication.

This current study showed that pre-existing glaucoma was significantly associated with graft failure ($P < .001$) (Table 8). This is consistent with the findings of the 2015 CDS group, which reported that preoperative glaucoma, particularly prior surgical glaucoma treatment in pseudophakic/aphakic corneal edema eyes, were associated with early failures.[11]

The primary purpose of this study was to evaluate longer-term PK graft survival as well as to study the impact of donor factors on graft failure. Glaucoma and glaucoma surgery as a risk factor for failure were analyzed and discussed in the present authors' earlier publications. In a study examining preoperative risk factors for failure, multivariate analysis revealed the following 9 predictors of graft failure:



Survival time	Optical PBK		Optical FED		Optical Keratoconus		Optical Post Infectious Scar	
	N	%	N	%	N	%	N	%
1st year	280	89.8%	95	95.7%	121	99.2%	140	94.9%
5th year	69	47.2%	59	74.9%	72	99.2%	73	80.5%
10th year	23	34.7%	20	55.3%	46	97.4%	40	72.9%
15th year	10	33.0%	7	42.7%	23	94.7%	18	67.7%
20th year	-	-	-	-	8	94.7%	6	63.2%
Survival time	**Optical Corneal Injury**		**Tectonic Infectious Keratitis**		**Tectonic Non-infectious corneal melt/perforation**		**Therapeutic Infectious Keratitis**	
1st year	100	86.8%	20	83.6%	18	87.5%	77	70.4%
5th year	40	56.4%	1	55.7%	4	87.5%	17	63.7%
10th year	17	48.2%	-	-	-	-	6	54.6%
15th year	11	48.2%	-	-	-	-	-	-
20th year	3	40.2%	-	-	-	-	-	-

Log Rank test was conducted for p values.

Significant differences ($p < 0.05$)

Optical PBK vs Optical FED/keratoconus/optical post-infectious scar (p=0.000, p=0.000, p=0.000)

Optical FED vs Optical keratoconus/Tectonic infectious keratitis/therapeutic infectious keratitis (p=0.000, p= 0.013, p=0.016)

Optical keratoconus vs optical post infectious scar/optical corneal injury/tectonic infectious keratitis (p= 0.000, p=0.000, p=0.000, p=0.013, p=0.000)

Optical post infectious scar vs optical corneal injury/tectonic infectious keratitis/therapeutic infectious keratitis (p=0.001, p=0.040, p=0.000)

No significant differences for other survival curves comparisons.

FIGURE 5. Survival curves for PK by major diagnosis. FED = Fuchs' endothelial dystrophy; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty.

recipient sex, age, graft size, graft endothelial status, primary corneal disease, glaucoma, inflammation, perforation, and corneal vascularization.[6] In a subsequent study evaluating postoperative risk factors for failure following PK, multivariate regression analysis revealed postoperative infection and endophthalmitis, recurrence of primary disease, allograft rejection, repeated corneal graft, glaucoma surgery, and lid surgery as significant predictors of graft failure.[13]

Allograft rejection continues to be the single most important cause of graft failure despite improvements in PK techniques, as well as the availability of potent topical steroids.[14,15] Rejection and endothelial failure (which many times develops after a rejection due to the large number of endothelial cells lost during a rejection episode) remain the main causes of graft failure in several reported series.[4,5] Oral immunosuppression after PK is used only for high-risk corneal grafts (usually those with deep vascularization and for repeated grafts) but not routinely in low-risk, primary grafts because the side effects of systemic immunosuppression are believed to outweigh its possible benefits for graft survival. Oral immunosuppression does seem to improve the survival rates and rejection risk in high-risk PK, where either mycophenolate mofetil or cyclosporin A was usually administered postoperatively.[16,17] However, given the long-term systemic side effects of those medications, its routine use is not justifiable. Lamellar grafts (anterior lamellar and endothelial keratoplasty) have reduced several of those risks, and many studies are reporting lowered risk of rejection and glaucoma with lamellar corneal grafts compared to PK.[18–21]

Given reasonably good outcomes of PK procedures, specifically those performed for optical indications, PK will continue to have a role not only in therapeutic and tectonic grafts but also in optical grafts where there is both significant endothelial compromise and visually significant stromal scarring. With the advent and domination of the lamellar keratoplasty technique, the findings of this study needs further long-term corroboration and comparison vis-a-vis lamellar graft for similar indications.[22,23]

The limitations of this study include the fact that the present Asian cohort was different from other long-term PK cohorts and may make comparisons difficult. The smaller sample sizes at 10, 15, and 20 years' follow-up; insufficient data for prior glaucoma surgery for pre-existing glaucoma cases and peripheral anterior synechiae and insufficient postoperative endothelial cell count data available for analysis. Between 1991 and 1995, donor cornea eye banks did not have ECD information, and ECD data were obtained from different specular devices in the various eye banks. This could have influenced conclusions regarding donor ECD and the relationship to graft failure.

In conclusion, penetrating corneal graft survival decreased over time from 91% at 1 year to 44% at 20 years' follow-up. Graft survival was significantly better for optical grafts than therapeutic and tectonic grafts. Multivariate analysis suggests that a younger donor age and higher donor endothelial cell count are associated with better long-term graft survival for optical grafts. Preoperative diagnosis significantly affected graft survival. Keratoconus grafts had the best long-term survival rate. FED grafts had better survival rate than PBK grafts. High-risk factors were found in a higher percentage in PBK grafts and contributed to the low long-term survival rate. Pre-existing glaucoma was significantly associated with graft failure. Allograft rejection and late endothelial failure accounted for more than 60% of graft failures.

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