• Clinical Research •

Penetrating keratoplasty in children under 3 years old with congenital corneal opacities

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Abstract

● **AIM:** To evaluate the graft rejection and visual outcomes after penetrating keratoplasty (PK) in the presence of various congenital corneal opacities in children.

● **METHODS:** In this retrospective cohort study, children who underwent PK were then followed for 5y. The patient's medical records were collected from June 2014 until June 2019 and analyzed in December 2019. All patients were children under three years old with congenital corneal opacities with or without microcornea who came to a pediatric ophthalmologist and underwent PK in Jakarta Eye Center (JEC). Beforehand, all children have participated in a thorough evaluation for PK. In the case of severe microcornea was not advised to undergo surgery. The visual outcomes and graft survival rate were described in percentages. The graft survival plot was presented with Kaplan-Meier, while the visual acuity was analyzed using the Wilcoxon signed ranks test.

● **RESULTS:** Sixteen eyes from eleven patients (seven girls and four boys) underwent PK. The graft survival rate of the first 6, 12, and 18 mo later of keratoplasty was 100%, 83.3%, and 66.7%, respectively. The overall mean survival time is 22mo (standard error 2.419), and no significant difference between the patients underwent PK before and after 36mo of their age (P=0.52). The graft failure was 50%, and post-surgery complications included cataract 43.7%, band keratopathy 12.5%, and scleromalasia 6.25%. Wilcoxon test analysis of visual acuity post keratoplasty was not statistically significant (P=0.34), while overall showed 44% improvements of visual outcome for 5y of follow-up. With a good survival at one year up to 22mo (83.3%), the visual acuity could be achieved (63%), and showed improvements (44%) during follow-up.

● **CONCLUSION:** The complications are frequent for pediatric PK. Thus, corneal surgery on infants requires careful case selection, adequate pre-operative evaluation, skilled surgery (optical correction), very close cooperation family–physician, intensive post-operation care, and amblyopia management in the future.

● **KEYWORDS:** pediatric penetrating keratoplasty; congenital corneal opacities; microcornea; children
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INTRODUCTION

Penetrating keratoplasty (PK) has been the most challenging technique for pediatric and corneal surgeons since its first attempt in 1977 by Waring and Laibson, followed by Stulting in 1984, and Cowden in 1990, where they showed satisfying results. Although the prognosis is not as good as in adults, PK is still considered as the first step preventing irreversible loss of visual function in a child due to amblyopia. Several indications for pediatric PK, including congenital causes of corneal opacities, acquired traumatic and non-traumatic corneal opacities cases[1].

Early PK is mandatory to achieve optimal visual development and prevent the incidence of amblyopia. The prevalence of congenital corneal opacities is approximately 3/100 000. The leading cause of congenital corneal abnormalities in developed countries is Peter's anomaly (40.3%), followed by sclerocornea (18.1%), dermoid cyst (15.3%), microphthalmia (4.2%), birth trauma and metabolic diseases (2.8%). Studies reported previously that the range of indication for paediatric PK in cases of congenital diseases lasts from 14% to 64%, while in acquired non-traumatic condition is from 19% to 80%, and acquired traumatic disorders 6% to 29%[2].

The clinical outcome of PK varies from visual development and restoration, clarity of the graft, risk of rejection and infection, which indicates that corneal transplant is essential. During the period of visual development, visual rehabilitation is required after customized clinical and surgical management

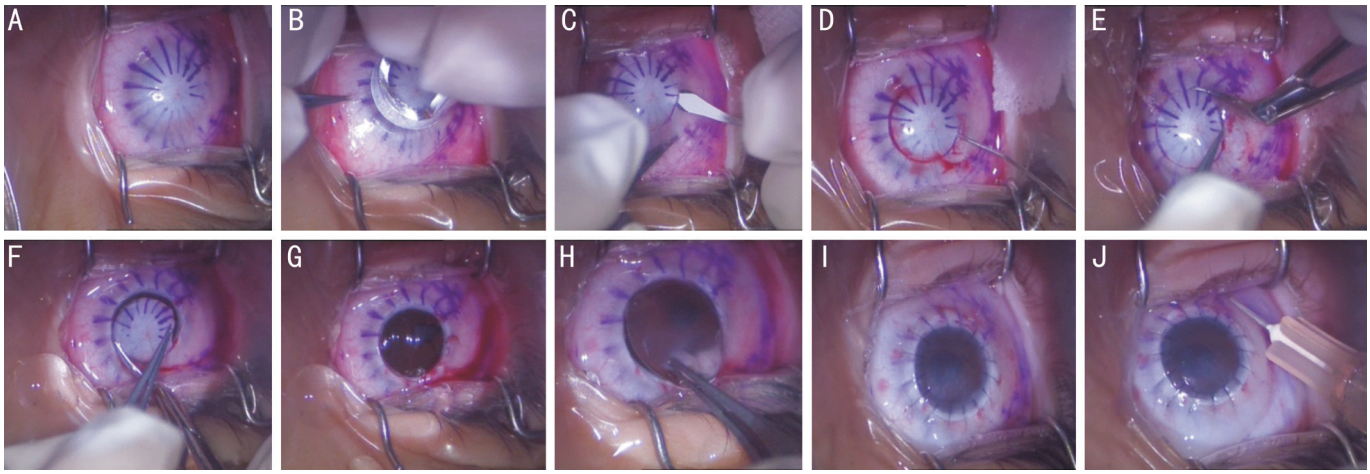

Figure 1 The surgical technique of penetrating keratoplasty A: Marked cornea; B, C: Trephination; D: Viscoelastic was injected behind the cornea, in front of iris-lens; E, F: Corneal scissors to excise entire cornea from right to left; G: Post excision of the corneal recipient; H: The donor graft was placed; I: Graft was sutured; J: Subconjunctival corticosteroid and topical antibiotic were added.

to overcome the significant challenges associated with pediatric keratoplasty[2-3]. In terms of facing the unique challenges of pediatric PK, the importance of pre-operative, intraoperative, and post-operative care should be considered[1].

Thus, this study aims to evaluate the survival of graft rejection and visual outcomes in five years of follow-up after PK in the presence of various congenital corneal abnormalities in children age less than three years old in Jakarta Eye Center.

SUBJECTS AND METHODS

Ethical Approval The ethical approval of this study was given by the Ethic Committee of Jakarta Eye Center and the consents were approved during the informed consent prior to surgery.

Patients Our study included children under three years old, referred by a pediatric ophthalmologist, which then cornea transplantation was performed by the cornea surgeon, between the year 2014-2019 in Jakarta Eye Center (JEC). The data were collected by a retrospective review of the patient's medical record with a cohort study design. Children with congenital corneal abnormalities were indicated to undergo surgery.

Pre-operative Care The importance of pre-operative care is to assess the possible benefits of the surgery outweigh the potential risks and all alternatives of PK have been considered[1]. The evaluation of pre-operative care comprised slit-lamp handled, tonopen, B scan Ultrasonography, fundus retcam, cornea diameter measurement, ERG-VEP, and retinoscopy. For a severe microcornea found during slit-lamp examination, then the PK was not advised. In case of cataract, the surgery can be done along with keratoplasty. An ocular pressure above 20 mm Hg found during the Icare® PRO tonometer examination should be referred to a glaucoma specialist. The ocular pressure and cornea diameter measurement can be evaluated under anaesthesia, or referred to as evaluation under anaesthesia (EUA). The ERG-VEP was done in EUA to evaluate the function of retina and brain. The results were then consulted to neuro-ophthalmologist to decide whether PK should be done or not. Retina examination is under B scan to evaluate the posterior segment. Retcam was done after keratoplasty to assess in case of opacity in the posterior segment. Afterwards, retinoscopy was done with dilated pupil.

Donor Cornea All cornea donors were from Santa Lucia Eye Bank, Philippines. The collected donor age was ranged from 17 to 23 years old. The cornea donor size was range of 7-7.5 mm in diameter. The regular cornea size of the recipients was expected to be ranged from 6.5-7 mm. The host-graft disparity was counted as 0.25-0.50 mm.

Surgical Technique All surgeries were performed under general anesthesia. The initial step was to remove the recipient's cornea by partial thickness trephination. A careful excision of the cornea was performed with curved corneal or Vannas scissors. Manual iridectomy was created in the upper iris to prevent the risk of glaucoma later after surgery. A viscoelastic was then required to reform the anterior chamber and protect the iris-lens. The graft was secured using 16 interrupted 10-0 nylon sutures with knots buried. Subconjunctival corticosteroid injection and topical antibiotics were given at the closure of surgery (Figure 1).

Postoperative Care The administration of antibiotic eyedrops was given hourly for the first week, then tapered off to six times daily for the next four weeks, followed by four times daily for five to six months. Frequent topical steroid is essential to reduce the high risk of rejection. The initial steroid eyedrops were added six times daily for the first four weeks, followed by slow tapered of four times daily for six months. Anti-glaucoma eyedrops were adjusted to administer topical steroids given the doses twice daily for four to six months.

Table 1 Results and follow-up after penetrating keratoplasty

No.	Age (mo)	Eye	VA preop.	Age PK done (mo)	LoFU (mo)	LoFU in total (mo)	IOP	Graft	Rejection	Time of rejection (mo)	Other findings postop.	Time to failure (mo)	VA postop.
1	13	OS	LFOF	19	36	55	21	Clear			Band keratopathy	24	LFOF
2	12	OD	LF	29	7	33	20	Clear					LFOF
3	12	OS	LF	15	21	33	17		(+)	7	Cataract	20	(-)
4	12	OD	LF	22	22	31	19		(+)	9			(-)
5	12	OS	LF	14	14	31	13	Clear					LFOF
6	4	OD	Refuse	19	17	29	14		(+)	13	Cataract	13	LF
7	24	OD	Refuse	24	14	14	17	Clear					0.2
8	5	OD	LF	15	5	15	14	Clear					LFOF
9	36	OD	LFOF	46	4	12	18	Clear					LFOF
10	15	OD	LFOF	33	15	28	10	Clear					LFOF
11	15	OS	LFOF	19	28	33	19	Clear			Cataract scleromalacia	21 23	Refuse
12	4	OD	Refuse	18	11	18	9	Clear					Refuse
13	3	OD	Refuse	19	13	32	21	Clear			Cataract	5	LFOF
14	3	OS	Refuse	27	12	32	22	Clear			Cataract	2	LFOF
15	36	OD	LFOF	56	24	30	14	Clear			Cataract	12	0.2
16	36	OS	LFOF	42	29	30	17	Clear			Cataract band keratopathy	14 10	0.15

Age: The age of the patient at the time of first visit; VA: Visual acuity; LoFU : Length of follow-up post-operative; LoFU in total: The total of follow up since initial until the last visit; IOP: Intraocular pressure; LF: Light fixation; OF: Object fixation. The age of the patients during the initial visit were between 3 to 36 months old. The visual acuity vary depends on the opacity, the age, and whether the child was cooperative during examination. The age when the penetrating keratoplasty was performed rely on the availability of the eye donor. Thirteen eyes showed clear grafts and three developed rejections in 7 to 13mo after keratoplasty. Graft failure occurred in two to 24mo after keratoplasty with the formation of band keratopathy, cataract, and scleromalacia.

At each post-operative visit in the office or under anesthesia, the examination of visual acuity and intraocular pressure (IOP) were measured. Additional slit-lamp handled was performed to assess the condition of the graft. The sutures were removed within four to six months after keratoplasty. Any loose sutures were removed immediately.

Statistical Analysis The visual acuity and graft survival rate in 6, 12, and 18mo were evaluated by descriptive statistics using percentages. We used Kaplan-Meier to present the graft survival plots showing the association between rejection and age. The survival curve included were age below 24mo and above 24mo when the PK was performed. The visual acuity before and after PK was also analyzed using Wilcoxon signed ranks test.

RESULTS

PK was performed in sixteen eyes from eleven patients, comprised of seven girls and four boys within 3 to 36 months old. The median age of the first visit was 12 months old. When the surgery was done, it was 14 until 56 months old, with a median age of 20.5 months old. The follow up was then conducted for patients four months after the surgery until 36mo post PK with the median time of 14.5mo. The total length of follow up was 12 to 55mo. The measured mean IOP was 16.5±3.9 mm Hg (Table 1).

All cases had congenital corneal opacification (CCO) with or without microcornea. Of all the patients, four had unilateral CCO, while seven cases were bilateral. PK was performed on both eyes of five cases of bilateral CCO. However, two eyes had severe microcornea, hence the surgery was not advised (Table 1).

Thirteen eyes of sixteen operated eyes showed clear grafts with no rejection in the next following months. The three grafts rejection manifested 7 to 13mo after the PK. The graft survival rate of the first 6, 12, and 18mo later of keratoplasty was 100%, 83.3%, and 66.7%, respectively, from 14 eyes (Figure 2). The two eyes had times of follow up before six months were excluded consequently. The subsequent two until 21mo, additional cataract surgeries were done in 7 eyes, which had developed a cataract. The other two eyes had band keratopathy after 10- and 24-months post keratoplasty. A scleromalacia occurred in one eye of a patient with cataract 23mo after surgery (Table 1).

The graft survival on Kaplan-Meier showed the time of rejection after the grafts were implanted (Figure 3). The groups were divided based on the type of rejection. Eventually, 7 eyes showed no rejection and graft failure at the given time. However, further follow-up not conducted later. Overall, the graft failures occurred in 50% of the operated eyes and post-surgery complications included cataract 43.7%; band keratopathy 12.5%, and scleromalacia 6.25%. However, the

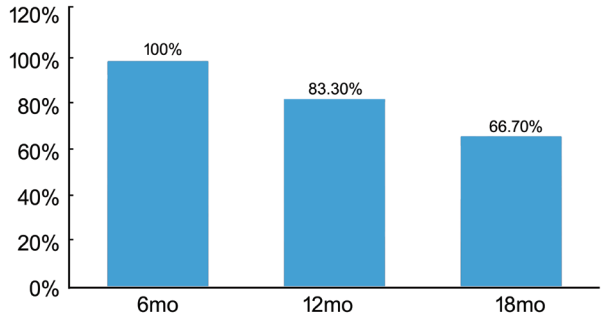

Figure 2 The graft survival rate after keratoplasty The graft survival rate of the first 6, 12, and 18mo after keratoplasty showed 100%, 83.3%, and 66.7% respectively, excluding two eyes with less than 6mo of follow-up.

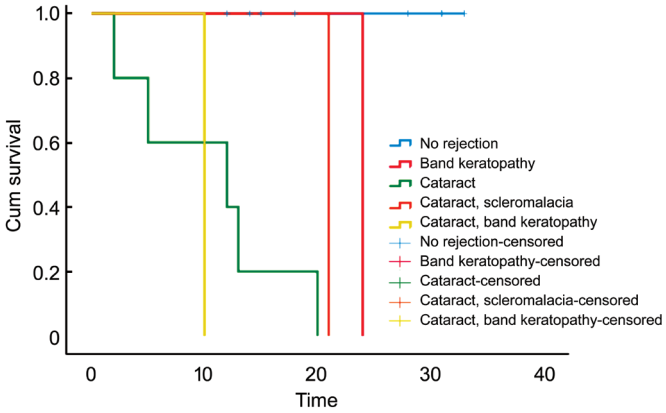

Figure 3 Kaplan-Meier graft survival Seven eyes showed no rejection and graft failure (blue), 5 eyes had cataract only (green), 1 eye had both cataract and scleromalacia (orange), 1 eye had both cataract and band keratopathy (yellow). Censored in no rejection and graft failure group means the time of last follow-up. Censored in graft failures showed the time in which they occurred.

overall mean survival time based on the aged timing of surgery before and after 36mo is 22mo (95% confidence interval, standard error 2.419) and no significant difference between the patient's age underwent PK before and after 36mo of their age (P=0.52).

The visual acuity of 7 eyes had improvement post keratoplasty, while six eyes were equal to pre-graft, and three eyes had reduced vision due to the effect of graft failure. In addition, the visual acuity of bilateral CCO, which the PK was done on both, had better outcomes than the unilateral CCO. The visual acuity pre- and post-graft analysis using the Wilcoxon test indicates not significant (P=0.34). Nonetheless, 44% had improvement in visual outcomes after PK (Figure 4).

A successful PK was performed in a girl with CCO on both of her eyes (Figure 5A). The keratoplasty was done one by one following the availability of the eye donor, in which the left was performed first. We managed the surgery on the right eye eight months later (Figure 5B, 5C). The evaluation six months later showed clear grafts on both eyes with no signs of rejection and graft failure (Figure 6).

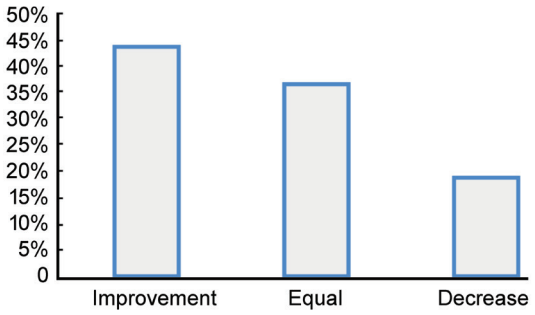

Figure 4 Visual acuity after penetrating keratoplasty The visual acuity after penetrating keratoplasty showed 44% of improvement, 37% were equal and 19% were decreased.

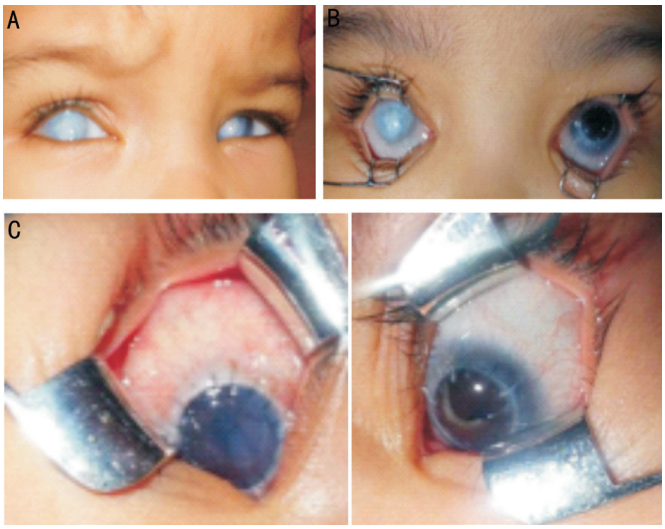

Figure 5 A 22-month-old girl with CCO on both eyes A: Before keratoplasty; B: 6mo after keratoplasty on the left eye; C: A day after keratoplasty on the right eye and eight months later of the left eye.

Figure 6 Clear grafts on both eyes Penetrating keratoplasty was done in both eyes, showing clear graft six months postoperative on the right eye. No signs of rejection and graft failure were found.

DISCUSSION

The development of visual acuity is critical, especially during rapid development in early ages, starting from neonates until the first six months of life. Vision development remains important during preschool years and affects the latter outcomes. Therefore, congenital disorder and trauma disrupt the process of development that would impact the visual system[4]. One of the leading causes of congenital disorders that affect the vision in children is CCO[5]. Thus, the primary aim of pediatric keratoplasty is to improve their visual acuity that was disrupted due to opacity.

A study by Zhang *et al*[5] reported that the most common indication of PK for children under 12 years old was CCO. The patients were categorized as infants (≥3mo and <4y) or children (≥4y and ≤12y). In our study, most patients came within the age of 12 to 36mo. Only five patients came before six months of age. Most parents may not recognize the signs and symptoms as they came later at age 12mo. However, the keratoplasty was done at six months up to a year after the initial visit due to the availability of the eye donor. Most PK was done during infants, while the other three eyes were performed in 42, 46, and 56mo.

No consensus is available among studies to provide the optimal timing of keratoplasty. However, most studies found that infants (<5y) presented poorer graft survival than children aged 5-12y and aged 13-19y. Treatment of amblyopia is the most significant factor predictive of visual improvement postoperatively. On the contrary, complications can be prevented with frequent visits and cooperation between practitioners and patients[3]. As mentioned in this study, the eldest age of the patient for surgery is 54mo, in which complication occurred 12mo later but showed improvement of visual acuity. Although the age gap of patients in this study had no significant difference that reflects the results (P=0.52), the keratoplasty successfully delivered a clear graft in the first year. We believed that performing keratoplasty in infants early, especially in bilateral cases, may help improve and develop their visual acuity during that time. Further follow-up, close monitoring, and visual rehabilitation can reduce the severity of amblyopia in the future.

Our study reported three eyes that had a rejection in 7 to 13mo after keratoplasty. Further findings such as band keratopathy, cataract, and scleromalacia were developed later as graft failure. Patients were followed 12 to 56mo after surgery and advised for routine examination and rehabilitation as graft failure can occur later. We suspected that other conditions such as usage of topical steroids, autoimmune or genetic disease disrupted the graft. The PK done by Huang[6] reported that infants frequently have a concomitant eye disease, which requires simultaneous or subsequent procedures, leading to much higher rates of graft rejection. Therefore, managing keratoplasty, especially in children age two years old, is challenging.

Graft rejection, ocular trauma on graft, and inflammation can occur as the complications of keratoplasty in children[7]. Further post-operative failures such as cataracts can be caused by prolonged use of steroid medication[8]. However, the formation of band keratopathy and scleromalacia are yet unknown in this study. Several theories are upsurged to understand pathogenesis. Band keratopathy may be related to renal liver dysfunction, increase serum calcium and phosphate, inflammation, or infection, and intracameral viscoelastic substance[9-10]. As for scleromalacia, a metabolic disturbance may also play a role, such as rheumatoid arthritis and osteogenesis imperfecta. A recent study suggested the theoretical risk of corticosteroids to promote the thinning of the sclera[11].

A study previously conducted by Di Zazzo *et al*[2] conclude that rejection is not a significant predictor of graft failure as most of the graft rejection episodes were successfully treated. A successful restoration comprises a good timely treatment. The use of topical prednisolone 1.0%, or dexamethasone 0.1% drops, once per hour around the clock for one week with a gradual taper, and less potent steroid eye drop of fluorometholone in 3-6mo is also advisable. Systemic steroid therapy in the form of an intravenous pulse steroid (intravenous dexamethasone 4-5 mg/kg body weight, diluted in 150 mL of 5% dextrose over 30-60 min with monitoring of vital signs may also contribute. Oral systemic steroids (1 mg/kg body weight) can be prescribed after initial pulse therapy in tapering doses, although the efficacy is still unclear. An increased frequency of topical steroids and antibiotics is required for a week after suture removal. Topical cyclosporine (CsA) 2% four times a day, then tapered to twice daily, can reduce the frequency, duration, and subsequent side effects of postoperative topical steroids[2]. Another study combined topical steroids with 2% topical cyclosporine (CsA) and resulted in 88.9% of rejection-free and statistically significant (P=0.0465)[12]. In our study, topical steroid administration was also done and tapered off after six months. However, the systemic steroid was not given because of good compliance during treatment with topical steroids only and avoided the risk of systemic complication.

Poor visual outcomes can be expected in infants, even with clear grafts. The time of suture removal can be lengthened based on age to reduce the risk of graft rejection and infection[6]. Early refractive rehabilitation is initiated after suture removal following corneal transplantation as soon as possible. Spectacle correction or contact lenses are prescribed and changed as required by amblyopia therapy. Scheduled follow-ups must be monitored for good visual outcomes[2]. In this study, patients were not given contact lenses due to the risk of falling off and difficulty being removed. Eye rehabilitation using spectacle correction and occlusion therapy might be saved and help to reduce the risk of amblyopia. The treatments were adjusted for the long term, following the improvement of visual outcomes. Additionally, we remove the suture quickly when it is loose to prevent secondary infection and rejection.

One of the primary purposes of pediatric PK is to prevent visual loss from amblyopia and maintain a better visual outcome[1]. A study by McClellan *et al*[13] showed that visual outcome after corneal transplantation is significantly worse

in patients with CCO. Amblyopia associated with CCO is a critical determinant of final vision after surgery. Patients with better visual acuity outcomes or equal following to keratoplasty enable them to develop an ambulatory vision in the presence of amblyopia.

A study in Mexico showed the mean graft survival time was 45.6mo (95% confidence interval 31.8-58.4mo, standard deviation 0.069), with a survival rate of 70% at one year[8]. Univariate Cox proportional hazard showed that being <9 years of age at the time of the surgery (P=0.023) and corneal dystrophies (P=0.04) were prognostic factors for corneal rejection[14]. A 10-year study in Malaysia reported that 18.75% of children who underwent PK were successfully achieved the best-corrected visual acuity of 6/12 or better. A hazy graft was noted in 68.75% of patients and was attributed to graft rejection, glaucoma, and graft failure. Factors contributing to the graft's survival rate at a one-year post-operative period include the presence of vascularized cornea, intraocular inflammation, and combined surgery, which were significant (P<0.05)[15].

A retrospective study by Karadag *et al*[16] showed that the overall mean graft survival time was 45.2±5.8mo, with a survival rate of 75.7% at one year. The 1-year graft survival rate was 51.9% and 90.7% in eyes with and without glaucoma, respectively. Cox proportional hazards regression analysis demonstrated that the presence of glaucoma (P=0.014) and concurrent operation during primary keratoplasty (P=0.049) were independent prognostic factors for poor graft survival. On the other hand, it was also stated that there was no association between the age of primary keratoplasty (P=0.626) and operation before or after primary keratoplasty (P=0.800 and P=0.104, respectively) that affected with lower graft survival. Half of the patients were able to achieve ambulatory vision at the last follow-up.

Lin *et al*[17] had conducted PK in children aged 0-7 years old with congenital corneal opacities. Results showed that ambulatory vision (≥20/960) was achieved in 43 of 60 eyes (71.7%) at the last follow-up, and 14 eyes (23.3%) had visual acuities >20/260. The ambulatory vision (P=0.012) was achieved significantly higher in bilateral opacity eyes (88.5%) compared to unilateral opacity eyes (58.8%). There were no significant differences in visual acuity among the different follow-up subgroups (<12mo, 12-36mo, and >36mo after operation; P=0.928). Ten of the 14 eyes that achieved 20/260 vision had corneal astigmatism ≤3.00 diopters.

Our study suggested pre and post keratoplasty was not significantly improved (that although the visual acuity P=0.34), the graft survival rate was found to be promising. The overall mean survival time is 22mo (standard error 2.419), with a survival rate of 83.3% int one year. Although there is a gap between the aged of timing PK, we provide the possibility of improving the visual acuity (44%) with good survival. Moreover, we did achieve our main purpose to stabilize the visual function to prevent blindness. Since the patients in our study were below three years old, even with the following object or light fixation only is satisfying. In conjunction with our study, we found this to be similar to the previous studies mentioned above.

The major challenge of performing pediatric PK is the difficulty of obtaining clinical pre-operative and post-operative conditions to assess accurately since almost all the patients were uncooperative[2]. Our study required long-term follow-up with closed monitoring, and we found this to be challenging. Amid the COVID-19 pandemic, patients avoid coming to the hospital recently, and monitoring was approached by phone call and photos *via* handphone.

Furthermore, an ultrasound biomicroscopy (UBM) and B-scan ultrasonography are usually required for evaluating the eye anterior and the posterior segments, including measurement of the axial diameter. Such evaluations can prevent the risk of graft failure after surgery. However, our study faced this limitation due to the absence of UBM in our clinic. Other reported studies showed that a comprehensive eye examination could predict the visual prognosis following PK. These include additional assessment and implementation of corneal transplants in children, including corneal, glaucoma, retina specialists, a pediatrician, and a geneticist[18]. Further study associated with larger patients, advanced equipment, and different techniques is still needed to improve the outcomes of PK in infants and children.

In conclusion, pediatric PK is a challenge for corneal surgeons and pediatric ophthalmologist. The delayed procedure will affect the immaturity of the visual system that may lead to severe amblyopia. With a good survival at one year (83.3%) with 22mo of mean survival time, the visual acuity can be achieved (63%) and showed improvements (44%) during follow-up. The complications post pediatric PK are frequent, such as cataract, graft rejection and failure, band keratopathy and scleromalacia. Thus, the surgery on an infant or child requires careful case selection, adequate pre-operative evaluation, skilled surgery for optical correction, very close cooperation family-physician, intensive post-operative care, and post-operative amblyopia management. This study's limitation includes the absence of UBM and difficulty in evaluating endothelial cell density in children.

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Conflicts of Interest: Susiyanti M, None; **Mawarasti B,** None; **Manurung FM,** None.

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