Clinical and Graft Survival Characteristics of Optical Penetrating Keratoplasty at a Tertiary Care Center in Indonesia: A 4-Years Retrospective Study

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Abstract

Introduction: *Purpose, to evaluate patient demographic characteristics, indications and variables related to penetrating keratoplasty (PK) survival. Study design, this study was retrospective case series.*
Methods: *We trace all medical records of PK patients from 2015 to 2018 in Cipto Mangunkusumo Hospital Jakarta. The traced variables were indications of surgery, corneal vascularization, previous failed graft, glaucoma after PK, and other complication. PK survival rate is shown in the Kaplan Meier curve using SPSS v20.0.*
Results: *A total of 214 patients underwent PK (men 67.3%, woman 32,7%) with mean age of 42.11 (0-85) years were included in this study. Three most common indications of keratoplasty were corneal scar (32.7%), infectious corneal ulcer (25.5%), and failed graft (19.2%). The overall graft survival rate for PK is 61.7%. The mean graft survival time was 14.388 ± 0.580 months (95% CI; 13.252-15.524).*
Conclusion: *The graft survival rate for penetrating optic keratoplasty was 61.7%. Establishing an appropriate early diagnosis, reasonable surgical procedures, close monitoring, and early detection of complications with proactive interventions lead to better outcomes. Further research is needed to determine the relationship between the risk factors for corneal graft failure.*

Keywords: *Graft rejection, Graft survival, Kaplan Meier survival analysis, Penetrating keratoplast*

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Karakteristik Klinis dan Kesintasan Keratoplasti Tembus Optik di Layanan Tingkat Tersier di Indonesia: Studi Retrospektif 4 Tahun

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Abstrak

Pendahuluan: *Tujuan penelitian untuk mengevaluasi karakteristik demografi pasien, indikasi dan variabel yang berhubungan dengan kesintasan keratoplasti tembus (PK). Desain penelitian: Penelitian ini adalah seri kasus retrospektif.*
Metode: *Menelusuri semua rekam medis pasien PK dari tahun 2015 hingga 2018 di RS Cipto Mangunkusumo Jakarta. Variabel yang ditelusuri adalah indikasi operasi, vaskularisasi kornea, cangkok yang gagal sebelumnya, glaukoma setelah PK, dan komplikasi lainnya. Tingkat kesintasan PK ditunjukkan pada kurva Kaplan Meier menggunakan SPSS v20.0.*
Hasil: *Sebanyak 214 pasien yang menjalani PK (pria 67,3%, wanita 32,7%) dengan usia rata-rata 42,11 (0-85) tahun dilibatkan dalam penelitian ini. Tiga indikasi keratoplasti yang paling umum adalah bekas luka kornea (32,7%), ulkus kornea infeksi (25,5%), dan cangkok yang gagal (19,2%). Tingkat kesintasan cangkok keseluruhan untuk PK adalah 61,7%. Rerata waktu kelangsungan hidup cangkok adalah 14,388 ± 0,580 bulan (95% CI; 13,252-15,524).*
Kesimpulan: *Tingkat kesintasan keratoplasti tembus optik adalah 61,7%. Penetapan diagnosis dini yang tepat, prosedur bedah yang wajar, pemantauan ketat, dan deteksi dini komplikasi dengan intervensi proaktif mengarah pada hasil yang lebih baik. Penelitian lebih lanjut diperlukan untuk menentukan hubungan antara faktor risiko kegagalan cangkok kornea.*

Kata kunci: *Penolakan cangkok, Kelangsungan hidup cangkok, Analisis kelangsungan hidup Kaplan Meier, Keratoplast penetrasi*

Introduction

Penetrating keratoplasty (PK) or corneal transplantation is a corneal replacement surgery as the primary visual rehabilitation therapy for diseases that irreversibly damage the cornea.[1,2] Globally, around 216.6 million people have visual impairments, and 4.5 million have visual impairments due to loss of corneal clarity.[3] Corneal disease is the fifth leading cause of blindness globally, with nearly 50% of corneal blindness represented in Africa and East Asia.[4] In 2013, there was 3.7% of corneal blindness in individuals of productive age in Indonesia with bilateral blindness, which caused a significant decrease in quality of life.[5]

Keratitis is the main indication for penetrating keratoplasty in Asia, which is around 32.3%.[6] Meanwhile, in South America, Europe, Australia, Middle East and Africa, the main indication for keratoplasty is keratoconus.[6]

Studies regarding the graft survival of penetrating keratoplasty (PK) also vary widely between countries because it is closely related to preoperative corneal conditions and available donors. This study evaluates patient demographic and clinical characteristics related to PK outcomes. It shows the survival rate of PK at one year postoperative at Cipto Mangunkusumo Hospital (CMH), as keratoplasty tertiary care center in Indonesia.

Methods

This was a retrospective study in which data are taken from medical records of patients undergoing PK at CMH, from 2015 to 2018. All subjects who met the inclusion criteria were recorded but incomplete medical records and patients who were not followed up through 3 months were excluded. All procedures conducted in studies were in accordance with the 1964 Helsinki declaration.

We classified the surgical indications or preoperative diagnosis into 10 groups: infectious corneal ulcer, keratitis HSV, chemical trauma, corneal scar, corneal dystrophy, keratoconus, bullous keratopathy, non-infectious corneal ulcer, failed graft, congenital disorder and adherent leucoma. In addition to specific clinical diagnosis, cases were also classified into 3 primary medical indications for transplantation: optical (surgery performed primarily to restore corneal clarity or for optical reasons), therapeutic (surgery performed to eradicate corneal infection or neoplasia), or tectonic (surgery performed primarily for tectonic globe integrity for impending or presenting corneal perforation).

Outcome measures were graft clarity. Graft clarity was graded as Grade 4 if grafts were optically clear with an excellent view of iris details, Grade 2-3 (borderline) if there was moderate to significant corneal haze with or without good view of iris details, and Grade 1-0 (failed) for opaque grafts with poor view of iris and anterior segment details. Graft failure was defined as irreversible loss of optical clarity with the date of onset taken when the patient presented to the cornea clinic with signs of irreversible rejection (for 3 months or more) or with failed graft. 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. Secondary glaucoma defined as glaucoma that occurred post-keratoplasty, which IOP more than 21 mmHg. In this study, we limit the discussion about graft survival and did not evaluate the treatment of the complication. All data were analyzed using SPSS software ver. 20.0. Survival analysis was performed using the Kaplan-Meier curve.

Results

A total of 214 eyes who underwent PK (men 67.3%, women 32,7%) with a mean age of 42.11 (0-85) years were found in this study (Table 1). There was no patient that underwent bilateral keratoplasty.

Table 1. Demographic Profile of PK Patients

Variables	N (%)
Sex	
Male	144 (67.3)
Female	70 (32.7)
Age Group (years)	
< 21	38 (17.8)
21 – 40	55 (25.7)
40 – 60	84 (39.3)
> 60	37 (17.3)

Clinical characteristics of recipients and the number of survived graft after one year are presented in Table 2. Patients with underlying disease such as glaucoma were exclude from this study. It showed that the three most common indications of keratoplasty were corneal scar (32.7%), infectious corneal ulcer (25.5%), and failed graft (19.2%). In this study, the one-year graft survival rate with Kaplan-Meier analysis for optical PK was 70,2%.

Postoperative complications or interventions determine the survival of the corneal graft. The most common complication in this study was secondary glaucoma (16.8%).

The overall graft survival rate for PK is 61.7%. The mean graft survival time was 14.388 ± 0.580 months (95% CI; 13.252-15.524).

Discussion

The difference in proportions between men and women varies across studies. Our data show a significantly higher number of males (67.3%), since the most common pre-operative diagnoses are corneal scar and corneal infection, we assume that men are more prone to the risk of infection or trauma. The age distribution in this study is quite similar to other studies. Arya, et al[7] and Joshi, et al[8] show the mean age of the participants is around 48-55 years. Another study by Chaudhry, et al[9] study has lower mean recipient age which is 34.5 years

The three most common indications for keratoplasty in this study are corneal scar, infectious corneal ulcer, and failed graft. Cornea infection seems to be the most common cause of corneal opacity in Indonesia despite the scarcity of cornea donor problems. Same with our result, the study by Arya, et al[7] in North India, Joshi, et al[8] in West India, and the similar result in Pakistan.[9] Study in Singapore

Table 2. Recipient's Clinical Characteristics (n=214)

Variables	Total	Graft survival (1 year)	
	n (%)	Yes n (%)	No n (%)
Indication			
Therapeutic	59	22	37
Infectious corneal ulcer	59 (27.5)	22 (37.2)	37 (62.7)
Tectonic	4	4	0
Chemical trauma (all grade)	4 (1.9)	4 (100)	0 (0)
Optical	151	106	45
Corneal scar	70 (32.7)	47 (67.1)	23 (32.8)
Corneal dystrophy	8 (3.7)	8 (100)	0 (0)
Keratoconus	2 (0.9)	2 (100)	0 (0)
Bullous keratopathy (pseudophakia/aphakia)	24 (11.2)	20 (83.3)	4 (16.7)
Failed graft	41 (19.2)	24 (58.5)	17 (41.4)
Congenital disorder	2 (0.9)	2 (100)	0 (0)
Adherent leucoma	3 (1.4)	2 (66.7)	1 (33.3)
Non-infectious corneal ulcer	1 (0.5)	1 (100)	0 (0)
Corneal neovascularization			
Absence	54 (25.2)	23 (42.6)	31 (57.4)
Quadrant 1	31 (14.5)	20 (64.5)	11 (35.4)
Quadrant 2	40 (18.7)	36 (90.0)	4 (10.0)
Quadrant 3	71 (33.2)	41 (57.7)	30 (42.2)
Quadrant 4	18 (8.4)	12 (66.7)	6 (33.3)
Graft Status			
First	173 (80.8)	108 (62.4)	65 (37.5)
Second or more	41 (19.1)	24 (58.5)	17(41.4)
Complication			
Absence	139 (64.9)	103 (74.1)	36 (34.9)
Glaucoma	36 (16.8)	21 (58.3)	15 (41.7)
Glaucoma + GDD[a]	12 (5.6)	7 (58.3)	5 (41.7)
Infected graft	18 (8.4)	0	18 (100)
Infected graft ++[b]	7 (3.3)	1 (14.3)	6 (85.7)
Endophtalmitis	2 (0.9)	0	2 (100)

[a]*GDD: glaucoma drainage device;* [b]*Infected graft ++: multiple complication*

found a different trend in the indications for PK which were previous graft failure, non-HSV corneal scarring, and bullous keratopathy.[7,8,11]

The Cornea Donor Study (CDS) found an increasing trend of graft failure in recipients 70 years of age or older compared to those younger than 60 years (29 vs 19%; p = 0.04).[10] The highest percentage of graft failure was found in patients with corneal scar, infectious corneal ulcer, and failed graft. Patients with non-infectious surgery indications had a higher percentage of graft success than infections. Recipients with non-HSV disease and HSV infection are included in keratoplasty at high risk of graft failure, so it is natural for graft failure to occur.[12,13] Keratoconus has a good percentage of graft success compared to cases with a history of infection and trauma (Hazard ratio = 1).[11] Avascularity, absence of intraocular inflammation and glaucoma, and intact endothelium in keratoconus and environmental dystrophy are favorable conditions for graft success.[12,13]

Chow, et al[12] reported that corneal grafts which considered to have high rejection risk were history of rejection before (n=12, 34%), two or more stromal vascularization (n=9, 26%), perforation or inflammation while surgery is performed (n=15, 34%), ato-

Table 3. Corneal Neovascularization (n=214)

	Graft survival (1 year)	
	Yes	No
	n (%)	n (%)
None	23 (42.6)	31 (57.4)
Neovascularization	109 (68.1)	51 (31.9)

p-value: 0.001

Table 4. Graft Status (n=214)

	Graft survival (1 year)	
	Yes	No
	n (%)	n (%)
First	108 (62.4)	65 (37.5)
Re-graft	24 (58.5)	17 (41.4)

p-value: 0.551

py (n=14, 40%), and large graft (diameter >9 mm; n=10, 29%). Anshu, et al[14] also reported that post-operative factors that lower graft survival were signs of infection, rejection, inflammatory processes due to recurrence of previous disease, and glaucoma surgery.

Patients with the characteristic finding of neovascularization experienced a graft failure rate of 31.9%. The incidence of graft failure was also higher in patients with neovascularization than in patients without neovascularization (p=0.001). This result is consistent with a study in India showing that patients with a vascularized cornea had a 51% higher risk of failure when compared to those without vascularization. Graft survival in the vascularized cornea was 18.55 and 22.69 months in the avascular cornea.[8] The Singapore Corneal Transplant Study (SCTS)[11] also reported a statistically significant difference (p = 0.017) in lower graft survival in vascularized versus non-vascularized corneas, same with this study (p=0.001). Another study divided low risk and high risk by evaluating the area involved in corneal vasculature.[7] In this study, evaluation of the area of vascularization was divided into 5 categories: no vascularization (absence), 1 quadrant, 2 quadrants, 3 quadrants, and 4 quadrants. We found the results were statistically different between vascularized versus non-vascularized corneas (p=0.001).

In this study, patients with a history repeated keratoplasty had higher graft failure rate (41.4%) compared to the first keratoplasty (37.5%). Kitazawa, et al[15] reported graft failure after repeated keratoplasty cause immunocompetent patient's condition was due

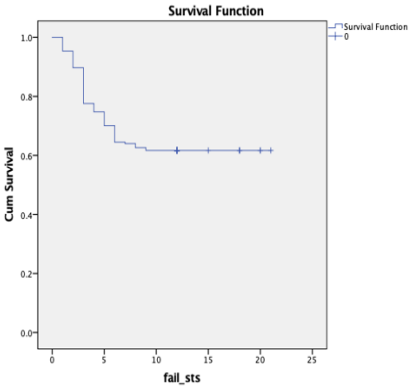

Figure 1. Overall Graft Survival Rate

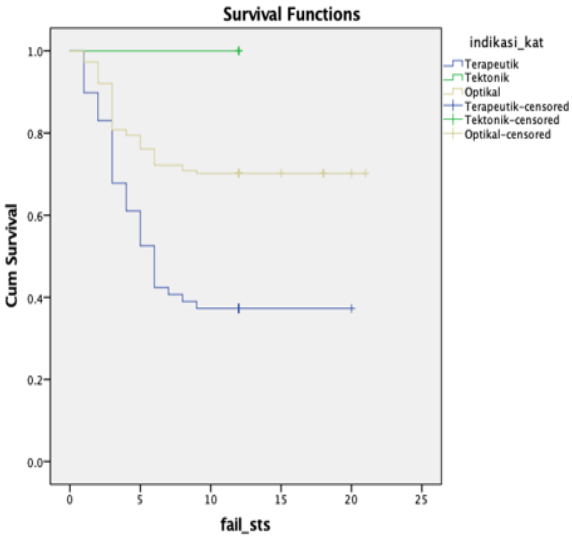

Figure 2. Graft Survival Rate Based on Indication

to the reduced immune privilege and camera oculi anterior cornea, thus increasing the risk of graft rejection.

Postoperative risk factors play a more significant role in long-term graft survival compared to preoperative risk factors, and lack of attention to the management of complications that arise further reduces long-term graft survival. the critical variable of patient 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, is a factor that also threatened to compromise the surgical outcomes. The most important bias introduced by the retrospective nature of this study is incomplete follow-up among all patients and differential follow-up between the surgical groups.

In this study, the highest incidence of complications in post-PK patients is glauco-

ma. Alvarenga, et al[16] reported that patients with a previous history of glaucoma or GDD had an increased incidence of graft failure (Hazard ratio = 6.8).[16]

In this study, the graft survival rate for penetrating optic keratoplasty was 61.7%, while the overall survival rate is 70% at one-year follow-up. The optical keratoplasty survival rate is lower than reports from developing countries. According to the Australian Corneal Graft Registry (ACGR) study,[17] graft survival probabilities after penetrating keratoplasty were 87%, 73%, 60%, and 46% at 1, 5, 10, and 15 years respectively. In the Singapore Corneal Transplant Study (SCTS) 11 in Asian patients, the graft survival rate with Kaplan-Meier of optical PK was 86.6%; 72.0%; 63.7%, and 52.0% at 1, 3, 5, and 10 years; respectively; survival rates for therapeutic grafts were 78.4%, 58.3%, and 37.3% at 1, 3, and 5 years and those for tectonic grafts were 68.3% and 41.7% at 1 and 3 years. In contrast to the results, Joshi, et al[8] reported a graft survival rate at the follow-up optical keratoplasty 1 and 2 years respectively to 65% and 52.5% in the West Indies. Moreover, other studies in North India by Arya, et al[7] also showed a lower value than the research, equal to 67.33% in the follow-up of 1 year and 59.4% at two years follow-up on keratoplasty optical invisibility.

Conclusion

In summary, the survival rate is less than 70% which is a bit lower than reports from most developed countries. Establishing an appropriate early diagnosis, reasonable surgical procedures, good donor quality, close monitoring, early detection of complications and proactive interventions can lead to better penetrating keratoplasty outcomes. Further research is needed to determine the relationship between risk factors for corneal graft failure.

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Conflict of interest

All Authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

All procedures conducted in studies were in accordance with the 1964 Helsinki declaration. For this type of retrospective study, formal consent was not required. The identifying particulars of participants were not revealed in the study.

References

1. Brad B. Cornea. In: Kanski's clinical ophthalmology a systemic approach. 8th ed. China: Elsevier; 2016. p. 168–237.
2. Chan CC, Perez MA, Verdier DD, Meter WS Van. Penetrating keratoplasty: the fundamentals. 4th ed. Cornea. Elsevier Inc.; 2017. p. 1264-1276.
3. Mathews PM, Lindsley K, Aldave AJ, Akpek EK. Etiology of global corneal blindness and current practices of corneal transplantation: a focused review. Cornea. 2018;37:1198–203.
4. Sieving P, Lambrou G, Gichuhi S, Huang J, Hejtmancik J, Zheng Y, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Heal. 2017;5:e1221–34.
5. Asrorudin M, Artini W, Gondhowiarjo TD, Rahayu T, Lestari YD. Impacts of impaired vision and eye diseases on vision-related quality of life in Indonesia. Makara J Heal Res. 2017;23:104–10.
6. Matthaei M, Sandhaeger H, Hermel M, Adler W, Jun AS, Cursiefen C, et al. Changing indications in penetrating keratoplasty: A systematic review of 34 years of global reporting. Transplantation. 2017;101:1387–99.
7. Arya SK, Raj A, Bamotra RK, Bhatti A, Deswal J, Sindhu M. Indications and graft survival analysis in optical penetrating keratoplasty in a tertiary care center in North India: a 5-year study. Int Ophthalmol. 2018;38:1669–79.
8. Joshi S, More P, Deshpande M, Jagdale S. Outcome of optical penetrating keratoplasties at a tertiary care eye institute in Western India. Indian J Ophthalmol. 2011;60:15.
9. Chaudhry TA, Sadiq SN, Sirang Z, Syed MA, Kamal M, Ahmad K. A 10-year review of indications for penetrating keratoplasty in a tertiary care setting in Karachi Pakistan. J Pak Med Assoc. 2016;66 3: S84–6.
10. Sugar A. Factors associated with corneal

graft survival in the cornea donor study. JAMA Ophthalmol. 2015;133:246–54.
11. Lim LS, Chan Y-H, Tan DTH, Htoon HM, Janardhanan P, Zhou H, et al. Penetrating keratoplasty in asian eyes. Ophthalmology. 2007;115:975– 982.e1.
12. Chow SP, Cook SD, Tole DM. Long-term outcomes of high-risk keratoplasty in patients receiving systemic immunosuppression. Cornea. 2015;34:1395– 9.
13. Bajracharya L, Gurung R. Outcome of therapeutic penetrating keratoplasty in a tertiary eye care center in Nepal. Clin Ophthalmol. 2015;2299.
14. Anshu A, Lim LS, Htoon HM, Tan DTH. Postoperative risk factors influencing corneal graft survival in the singapore corneal transplant study. Am J Ophthalmol. 2011;151:442–448.e1.
15. Kitazawa K, Wakimasu K, Kayukawa K, Yokota I, Inatomi T, Hieda O, et al. Moderately long-term safety and efficacy of repeat penetrating keratoplasty. Cornea. 2018;37:1255–9.
16. Alvarenga LS, Mannis MJ, Brandt JD, Lee WB, Schwab IR, Lim MC. The long-term results of keratoplasty in eyes with a glaucoma drainage device. Am J Ophthalmol. 2004;138:200–5.
17. Williams KA, Lowe M, Bartlett C, Kelly T-L, Coster DJ. Risk factors for human corneal graft failure within the Australian corneal graft registry. Transplantation. 2008 Dec;86:1720–4.