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Original Article

Retrospective analysis of corneal transplantation: a tertiary hospital database study over ten years

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Abstract: *Aim:* The clinical data from a tertiary hospital in Shanghai, China, were retrospectively analyzed to explore indications and changes in corneal transplant way, and the influencing factors related to the rate of re-graft in corneal transplantation in the past decade. *Material and Methods:* From July 1, 2005 to June 30, 2015, it was retrospectively analyzed that the clinical records of 772 patients (804 eyes) receiving corneal transplantation surgery from the ophthalmology center of a tertiary hospital, Shanghai, China. *Results:* A total of 772 patients (n = 804 eyes) received corneal transplantation at the Shanghai Tenth People's Hospital over the past 10 years. The top four indications for corneal transplantation were keratoleukoma after acute or chronic keratitis (n = 253, 31.47%), re-graft (n = 142, 17.66%), ocular trauma scar (n = 116, 14.43%), and corneal endothelium decompensation (n = 80, 9.95%). The major type of transplantation was penetrating keratoplasty, including simple penetrating keratoplasty and combination of penetrating keratoplasty with anterior or posterior segments (n = 708). In recent five years, an increasing number of lamellar keratoplasty was performed. In multivariate logistic models, re-graft was significantly correlated with way of transplant ($p<0.05$) and size of graft ($p<0.001$). *Conclusion:* Based on the 10-year clinical records from the single ophthalmology center, the main indication for corneal transplantation was keratoleukoma caused by acute or chronic infectious keratitis. The lamellar keratoplasty became popular. The re-graft was significantly correlated with transplant way and graft size, which proposed that they might be potential influencing factors to explain transplant rejections.

Keywords: Corneal transplantation, indication, surgical way, re-graft, transplant rejection

Introduction

Corneal transplantation, or keratoplasty, is a surgery that uses full-thickness or lamellar transparent cornea to replace the whole layer of opaque or diseased part of cornea to achieve treatment of corneal diseases. The first successful human corneal transplantation was achieved by Dr. Eduard Zirm in 1905 [1], which opened the development and improvement of corneal transplantation. Today, corneal transplantation became an efficient treatment for corneal diseases. Patients who had serious visual impairment because of corneal diseases could recapture vision by receiving corneal transplantations. Indication researches for corneal transplantation were developed globally. Based on reports from America and Europe, main causes for corneal transplantation included corneal endothelium dystrophy, pseudophakic bullous keratopathy, re-graft, and keratoconus [2-5]. The indication slightly varied in the Australia with mostly due to keratoconus, and then caused by re-graft, pseudophakic bullous keratopathy, and corneal dystrophy [5]. The main causes for corneal transplantation in Asia or developing countries mainly included infectious corneal diseases, ocular trauma scar, and keratoconus [6]. Because the absent of blood vessels in corneal under normal circumstance, or called "immune pardon" condition, the survival rate for corneal transplantation was much higher than other allogenic tissue transplantations. Beckingsale reported that the 10-year overall survival rate for corneal transplantation was 66% [7].

Table 1. Distributions of indications on corneal transplantation

Pathogeny	Number of eyes (n, %)		
	The first five years (July 2005 to June 2010) (n, %)	The last five years (July 2010 to June 2015) (n, %)	The whole ten years (July 2005 to June 2015) (n, %)
Ocular trauma	51, 12.91%	65, 15.89%	116, 14.43%
Infectious keratoleukoma	48, 12.15%	58, 14.18%	106, 13.18%
Old keratoleukoma	80, 20.25%	67, 16.38%	147, 18.28%
Corneal endothelial decompensation	36, 9.11%	44, 10.76%	80, 9.95%
Keratoconus	26, 6.59%	40, 9.78%	66, 8.21%
Corneal degeneration and dystrophy	32, 8.10%	29, 7.09%	61, 7.59%
Re-graft	84, 21.27%	58, 14.18%	142, 17.66%
Eye neoplasms	2, 0.51%	6, 1.47%	8, 1.00%
Iridocorneal endothelial syndrome	2, 0.51%	5, 1.22%	7, 0.87%
Unknown indication	34, 8.60%	37, 9.05%	71, 8.83%
Total	395, 49.13%	409, 50.87%	804, 100%

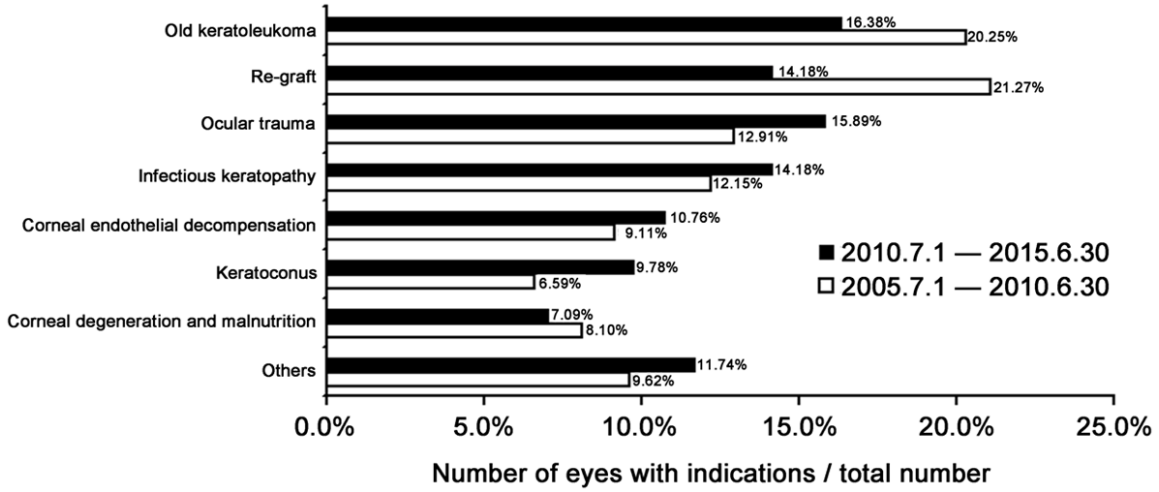

Figure 1. Spreadsheet for five-year change of indications (July 2005 to June 2010 vs. July 2010 to June 2015).

Because the indication and rejection of keratoplasty had regional and ethnic heterogeneity, and, to better guide the future corneal transplantation operations, the 10-year corneal transplantation clinical data, from one ophthalmology center in a tertiary hospital, Shanghai, China, were retrospectively analyzed to detect the corneal transplantation's indication and changing trend, also the risk factors for keratoplasty rejection.

Material and methods

Study participants

This study has been approved by the Ethics Committee of our Hospital. In the past 10-year (July 1, 2005 to June 30, 2015) study period, corneal transplant patients (n = 772, 804 eyes) at the Ophthalmology Center from the Shanghai Tenth People's Hospital were included. All operations were performed by the same surgeon. After excluding the patients for re-graft, 654 eyes were included for the further re-graft risk factor investigation.

Data collection

Well-trained ophthalmology physicians went through all the diagnostic cases that met inclusion criteria, and collected patients' information including name, gender, age, surgery eyes, diagnoses, indications, medical histories, preoperative corneal statuses and intraocular pressures, operation times, transplant approaches, graft's sizes, suture methods, re-operation or not, reasons for re-operation, transplantation times, etc.

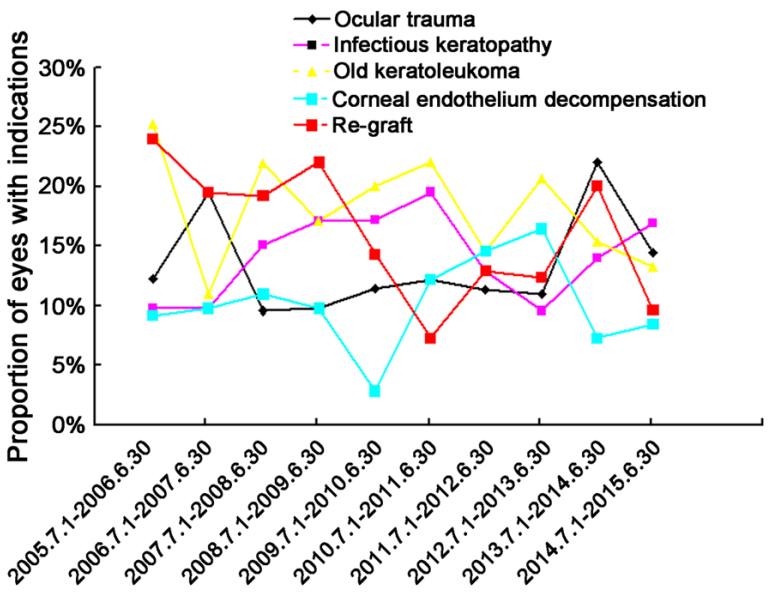

Figure 2. Line chart for the top five indications on corneal transplantation.

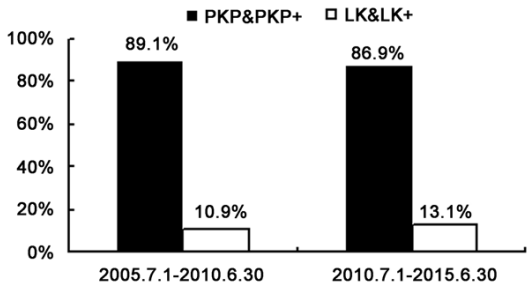

Figure 3. Ten year proportion of operation by PKP & PKP+ and LK & LK+ (PKP: Penetrating keratoplasty; PKP+: Penetrating keratoplasty combined with the ocular anterior or posterior segments surgery; LK: Lamellar keratoplasty; LK+: Lamellar keratoplasty combined with the ocular anterior or posterior segments surgery).

Statistical analysis

The patients' clinical information was all entered into the database. Quantitative data was presented as means ± standard deviation (X ± SD), and statistically described patients' demographic information, such as age and gender. The trend of change on corneal transplantation indication and transplant approaches were analyzed. The exposure was defined as transplantation frequency. Univariate analysis and multivariate logistic regression were used and adjusted for gender, age at first transplantation, indications, transplant approaches, graft's sizes, and suture methods. SAS 9.3 and Microsoft Excel were introduced in statistical analysis. $P<0.05$ was considered as statistically significant.

Results

From July 1, 2005 to June 30, 2015, 772 patients (804 eyes) recieved corneal transplantation. Among them, there were 493 males (63.86%) and 279 females (36.14%). The age group for all patients followed the normal distribution with most patients aging from 41 to 60 years old (36.32%), and mean age was 51.84 ± 18.84 years old (range: 1 to 89 years old).

10-year's change of indication

In the whole 10 years, the top four indications for corneal transplantation were keratoleukoma after acute or chronic keratitis (n = 253, 31.47%), re-graft (n = 142, 17.66%), ocular trauma scar (n = 116, 14.43%), and corneal endothelium decompensation (n = 80, 9.95%; **Table 1**).

From the five-year change of indication, the top five indications for the first five years (July 2005 to June 2010) were re-graft (21.27%), old keratoleukoma (20.25%), ocular trauma (12.91%), infectious keratopathy (12.15%), and corneal endothelial decompensation (9.11%). However, the top five indications for the second five years (July 2010 to June 2015) were old keratoleukoma (16.38%), ocular trauma (15.89%), infectious keratopathy (14.18%), re-graft (14.18%), and corneal endothelial decompensation (10.76%). Based on the changing rate, ocular trauma caused corneal transplantation decreased in general, but presented a transient increase around 2015 (year nine, 22.0%). Corneal transplantation due to infectious keratopathy showed an umbrella shape and reached the highest rate in 2011 (year six, 19.5%). Corneal endothelial decompensation waved rapidly with lowest rate at 2010 (year five, 2.9%), and then increased to the highest at 2013 (year eight, 16.4%), and decreased after that. Changing rate for old keratoleukoma had volatility with no linear trend observed. (**Figures 1** and **2**).

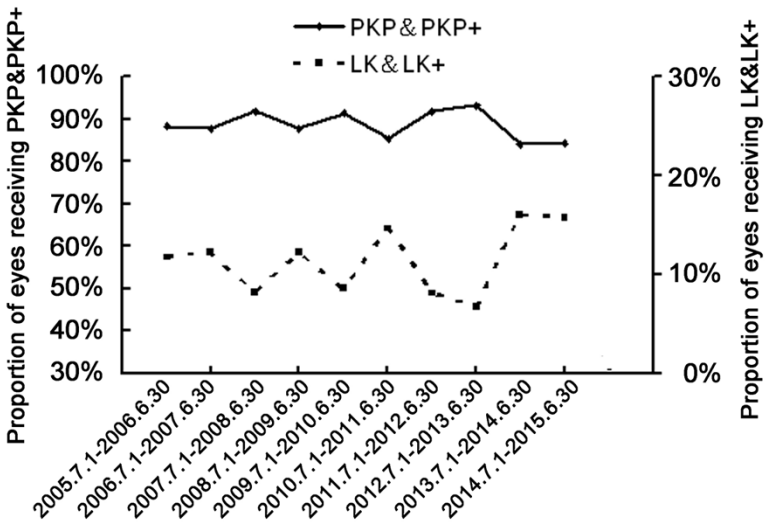

Figure 4. Annually changing pattern for PKP & PKP+ and LK & LK+ (PKP: Penetrating keratoplasty; PKP+: Penetrating keratoplasty combined with the ocular anterior or posterior segments surgery; LK: Lamellar keratoplasty; LK+: Lamellar keratoplasty combined with the ocular anterior or posterior segments surgery).

10-year's change of transplantation approach

In the five-year transplant approach changing analysis, the main approach was penetrating keratoplasty, including simple penetrating keratoplasty (PKP), and combination of penetrating keratoplasty with the ocular anterior or posterior segments (PKP+) with no significant changing in proportion during the 10-year study period as 89.1% for total corneal surgeries during the first five years and 86.9% during the last five years. The proportion of lamellar keratoplasty, including simple lamellar keratoplasty (LK) and combination of lamellar keratoplasty with ocular anterior or posterior segments (LK+) was 10.9% in the first five years and 13.1% in the last five years. The year-on-year changing pattern of corneal transplantation presented that the changing pattern for PKP & PKP+ varied slightly and remained as the main approach for corneal transplantation; however, though the proportion of LK & LK+ was small, the changing pattern showed an annually slow increase (**Figures 3** and **4**).

Risk factor analysis on 10-year transplantation

The univariate analysis showed that age ($p = 0.53$), gender ($p = 0.6$), and re-graft ($p = 0.06$) were not significantly related to transplantation frequency. However, operation times ($p = 0.01$), approaches ($p = 0.01$), and size of graft ($p<0.001$) were significantly correlated to the frequency of corneal transplantation (**Table 2**).

In the further multivariate regression models, the diameters of the grafts and operation approaches were significantly correlated to the surgery frequency (one time *vs*. more than one time) with $p<0.001$. If the diameters of grafts were ≥ 9 mm, the re-graft rate was significantly higher than other groups (OR = 2.96, 95% CI = 1.21-7.23). PKP+ group had a significant re-graft rate compared with other approach group (OR = 1.20, 95% CI = 0.60-2.43) (**Figure 5**).

Discussion

The indication for corneal transplantation varied from country to country, with the greatest variance between developing and developed countries. Patients for corneal transplantation from America and Europe were mainly caused by corneal endothelium dystrophy, pseudophakic bullous keratopathy and re-graft [2-5]. The indication of corneal transplantation in Australia was mostly due to keratoconus, and then caused by re-graft and pseudophakic bullous keratopathy [5]. In Asia, corneal transplantation was mainly caused by infectious corneal diseases, ocular trauma scar and keratoconus [6]. Our study found that, similar to other developing countries, the major indication of corneal transplantation in China were infectious corneal diseases/old keratoleukoma (31.47%), and then re-graft (17.66%), ocular trauma (14.43%), and corneal endothelium decompensation (9.95%). Keratoleukoma (infectious and obsolete), which was the primary cause of corneal transplantation in this study, was common sequelae of corneal lesions after corrupt the corneal stroma. Confirmed infectious keratoleukoma was 106 eyes, accounting for 13.18% of total cases, with 18.58% infectious caused by virus. The Herpes simplex virus keratitis was the major cause of the blinding corneal disease globally, with char-

Table 2. Distributions of clinical parameters in transplantation of frequency

Parameters	Transplantation frequency		*P*-value
	One time	> One time	
Age	50.81 ± 19.36	50.87 ± 18.49	0.53
Gender			
Male	301	113	0.6
Female	179	61	
Pathogeny			
Ocular trauma	76	40	0.06
Acute infectious keratopathy	30	12	
Old keratoleukoma	105	41	
Fungal keratitis	11	4	
Viral keratitis	34	13	
Corneal endothelial decompensation	58	21	
Keratoconus	54	12	
Corneal degeneration and dystrophy	48	10	
Eye neoplasms	6	1	
Iridocorneal endothelial syndrome	2	5	
Unknown indication	56	15	
Operation time			
2005.7.1-2010.6.30	209	97	0.01
2010.7.1-2015.6.30	271	77	
Surgical options			
LK	34	24	0.01
LK+	12	9	
PKP	399	129	
PKP+	35	12	
Graft size			
<7 mm	20	2	<0.001
7≤ X <8 mm	263	75	
8≤ X <9 mm	168	66	
≥ 9 mm	29	31	

acters such as easily misdiagnosis, difficult treatment and frequently reoccurrence [8].

Our study documented 116 eyes (14.43%) defined as ocular trauma scare, ranked the third major cause, which included ocular contusion, penetrating wounds, burns, acid-alkali chemical caused injury, and others, with male to female ratio equals to 51:7. Potential reason might be that the Yangtze River Delta region was industrial developed area with high risk of occupational-related eye trauma. If increasing the awareness of self-protection and improving the protection measures, ocular trauma scar cases would be reduced.

In present study, corneal endothelium decompensation (including bullous keratopathy) ranked the fourth causes in the 10 years. Among these patients, 86.25% had history of internal eye surgeries, of which 58.75% were cataract surgery. The cataract surgery maturely developed in the early 21st century. However, due to the lack of pre-operation endothelial dysfunction evaluation, variation in surgical technique and type of intraocular lens, and the number of operations, corneal endothelium decompensation occurred. As a result, improvement of pre-operation examination and evaluation of patients' ocular endothelium dysfunction before surgery would contribute to the decrease. In addition, careful selection of appropriate intraocular lens, the current intraoperative protection of corneal endothelium viscoelastic agent, and improvement and replacement for the artificial crystal could also limit damages. patients for endothelium decompensation were all treated by the PKP approach. Endothelial keratoplasty was limited by the technology and eager to be improved.

Though keratoconus was belong to the leading causes of corneal transplantation in developed countries [5], the proportion of keratoconus in this study remained small with only 8.21%. Compared between the first and last five years, proportion of the keratoconus patients increased during the last five years (6.59% in the first five years and 9.78% in the last five years). This change could not be explained by the theory that the keratoconus increased in general population. With the improvement of socioeconomic status, parents increased the attention on children's visual

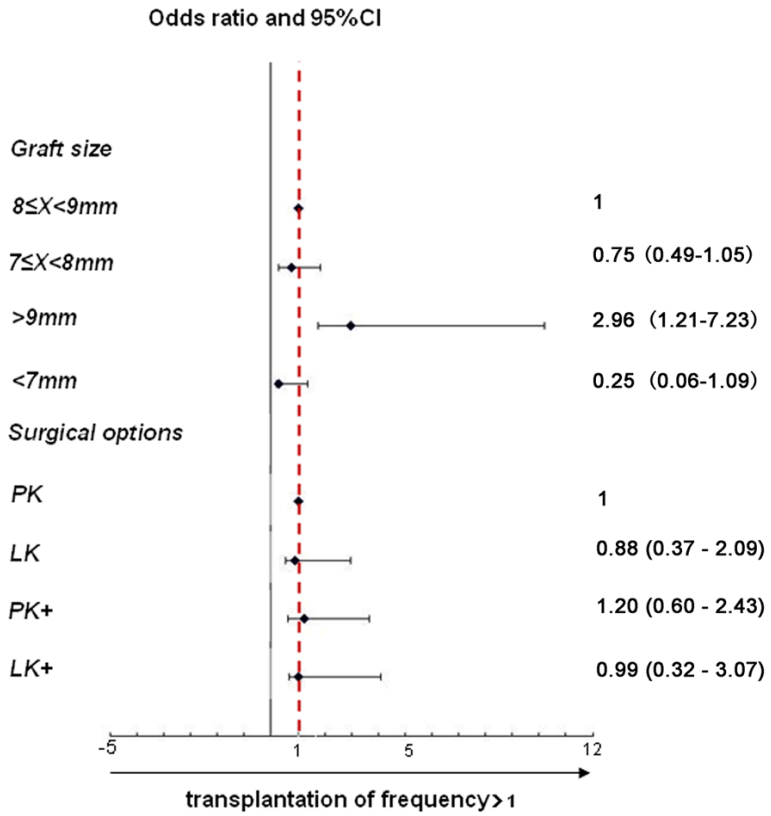

Figure 5. Comparison of transplantation of frequency at ten years (*one times vs. > one times*) adjusting for gender, age, operation times, graft sizes, and surgical options. (PKP: Penetrating keratoplasty; PKP+: Penetrating keratoplasty combined with the ocular anterior or posterior segments surgery; LK: Lamellar keratoplasty; LK+: Lamellar keratoplasty combined with the ocular anterior or posterior segments surgery).

acuity and quality and the understanding of keratoconus among physicians and technicians were also improved which helped more patients received the timely diagnosis and treatment.

Even though, corneal transplantation had a higher successful rate compared with transplantation of other tissues, post-operation rejection still troubled the ophthalmologists [9], ranked the second cause. The post-operation immune rejection was the major cause of corneal transplantation failure, especially among high-risk transplantation patients. If the rejection time appeared early and had a huge span, the rejection rate could be higher than 50%. The corneal transplantation rejection was a complex and continuous immune process [10, 11]. Normal cornea in the "immune pardon" stage was dependent on multiple factors, including no blood vessels, no lymphatic vessels, and relative lack of mature antigen presenting cells [12, 13]. The corneal immune reaction and the growing of new blood vessels after the operations could damage the "immune pardon" status [14-16].

The immune response promoted the silencing of antigen-presenting cells into the corneal stroma. Then, the tissue-compatible antigens on the surface of the donors' corneal cells were recognized by the host immune cell to cause immune waterfalls [17, 18]. The immune waterfalls promoted a variety of white blood cell infiltration, cytokines and inflammatory factors to release largely which caused corneal tissue hypoxia, and finally resulted in transplant rejection. In the host-induced corneal transplant rejection mechanism, the most important factor was the regeneration of the host corneal vascularization. In addition, rather than the total number of blood vessels, the degree of vascularization was based on the formation of vascular quadrant, so the deep matrix vascular regeneration was the main risk factor [19]. Jonas et al. observed that corneal vascularization before and after surgery was the most important risk factor for immunocompromised responses, with approximately 14% of patients with allogeneic PKP undergo rejection [20].

In the univariate analysis, after excluded patients with indication defined as "re-graft" and adjusting for age, gender, indication, transplant type, times of transplantation, size of grafts, and suture methods, a significantly correlation was detected between transplantation frequency (one time vs. more than one time) and transplant types, but not between transplant types and operation time. As a result, transplant types could be a potential risk factor. After further adjusting other potential confounders, transplant types were still strongly correlated with risk of re-graft, especially in PKP+ treatment (OR = 1.20, 95% CI = 0.60-2.43), and the association was gradually weak-

er for PKP, LK+, and LK. Traditional LK approach manually separated the front layer of the cornea of the matrix (shallow, deep) or posterior elastic layer and retained the posterior elastic layer and endothelial cell layer, which avoided the direct contact between allogeneic corneal graft and aqueous humor. The postoperative endothelial cell reaction was mild in LK, leading to a better return to vision. In our last five years analysis, LK approaches involved more in transplant type related to keratoleukoma, corneal degeneration, corneal dystrophy, and ocular surface tumors. With the continuous improvement of LK surgery, it would be possible to replace the PKP as the main transplant approach in treating the corneal diseases without significant lesions of endothelial cells.

This study included a variety of combined surgeries, which might lead to severe postoperative inflammatory response, with increased incidence of rejection. Moreover, size of grafts was significantly associated with transplantation frequency and operation time. After adjusted for confounders, the size of grafts and transplantation frequency presented a trend that the frequency increased significantly when the size of grafts increased, with the largest odds at the diameter of grafts ≥ 9 mm (OR = 2.96, 95% CI = 1.21-7.23). Large grafts were proved as a risk factor of rejection by previous studies. Because the larger the grafts were closer to the edge of corneal vascular and carried more allogeneic antigen components, which increased the risk of motivating the immune responses and had greater chance of rejection [21, 22]. As a result, though not enough evidences from clinical studies, we insisted that the diameters of grafts should be limited under 7.5 mm.

Based on this 10-year single center study, infectious corneal disease was still the major cause of corneal transplantation. Other common indications included re-graft, ocular trauma, and corneal endothelium decompensation. Keratoconus caused transplantation presented an increasing trend in the past decades. PKP & PKP+ remained as the major transplant approaches for corneal transplantation, whereas LK & LK+ showed a growing proportion. Transplant approaches and size of grafts were significantly correlated to the rate of re-graft. Though all our data was from the single ophthalmology center and had geographical limitation, we were still optimistic that the small diameter of the grafts with clean edge and deep LK approaches could reduce the rejection after transplantation and the frequency of re-graft.

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Disclosure of conflict of interest

None.

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