• Clinical Research •

Dynamic profile of ocular refraction in pediatric cataract patients after lens surgeries

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Abstract

● **AIM: To study the change in ocular refraction in patients with pediatric cataracts (PCs) after lens extraction.**

● **METHODS: A total of 1258 patients who were undergoing cataract extraction with/without intraocular lens (IOL) implantation were recruited during preoperative examinations between Jan 2010 and Oct 2013. Patient ages ranged from 1.5mo to 14y. Follow-ups were conducted at 1wk, 1, and 3mo postoperatively and every 3mo in the first year, then 6mo thereafter. Ocular refraction [evaluated as spherical equivalent (SE)] and yearly myopic shift (YMS) were recorded and statistically analyzed among patients with age at surgery, baseline ocular refraction, gender, postoperative time and laterality (bilateral *vs* unilateral).**

● **RESULTS: By Dec 31st 2015, 1172 participants had been followed for more than 2y. The median follow-up period was 3y. The critical factors affecting the ocular refraction of PC patients were baseline ocular refraction, postoperative time for both aphakic and pseudophakic eyes. YMS grew most rapidly in young childhood and early adolescence.**

● **CONCLUSION: After lens surgeries, ocular refraction in PC patients shows an individual difference of change. Further concerns should be raising to monitor the rapid myopic shift at early adolescence of these patients.**

● **KEYWORDS:** pediatric cataract; refraction; intraocular lens; myopic shift

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INTRODUCTION

Intraocular lens (IOL) implantation is currently a commonly used means of optically rehabilitating children undergoing cataract surgery. However, intriguing challenges remain in deciding the best IOL power to be implanted in a specific child. The major problem is that the variability of etiopathogenesis and treatment strategies for pediatric cataract (PC) increases the variability of ocular refraction among these patients. The postoperative/long-term refractive outcomes are not satisfactory among PC patients despite great efforts made by many investigators.

Anticipating a myopic shift of pseudophakic eye as a young child grows, several authors have recommended that an appropriate hyperopic range be established for children in the immediate postoperative period[1-2]. For example, the rate of refractive growth (RRG), which uses a semi-logarithmic model, is a formula designed to calculate the expected myopic shift in children[3-6]. However, some controversy still exists among physicians about the postoperative refractive goal. Some suggest that children should be made emmetropic after surgery so that the amblyopia treatment will be more effective or easily performed[7].

It is not our purpose to resolve this controversy. Instead, we seek to provide longitudinal refractive data from PC patients after lens removal to demonstrate the actual refractive change in a large cohort. In this study, we investigated the changing refractive status among 1258 PC patients (from 1.5mo to 14y at enrollment, average 5.5±4.9y). We aim to provide useful data from both aphakic and pseudophakic children to improve the determination strategy of IOL power in PC patients.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethical Review Committee of Zhongshan Ophthalmic Center, and the tenets of the Declaration of Helsinki were followed throughout this study. Written consent was obtained from patients' guardian.

Table 1 Arrangement of surgical strategies

Surgical indications	Age of patients (y)	Surgical strategies
Dense lens opacity in the visual axis, diameter >2 mm; non-dense lens opacity in the visual axis, diameter >2 mm, amblyopia and/or strabismus, or other significations of poor vision.	<2	I/A+PCCC+A-Vit
	2 to 3	I/A+IOL+PCCC+A-Vit
	>3	I/A+IOL+PCCC

I/A: Lens aspiration; PCCC: Posterior continuous curvilinear capsulorhexis; A-Vit: Anterior vitrectomy; IOL: Intraocular lens.

Enrollment Criteria Patients with PC who were undergoing cataract extraction with/without IOL implantation were recruited prospectively during preoperative screening at the Zhongshan Ophthalmic Center (ZOC), Guangdong, China, from January 2010 to October 2013 (clinical trial identifier: NCT02761850).

A patient was considered eligible upon meeting the following inclusion criteria: 1) patients diagnosed with congenital cataract or developmental cataract before surgery; congenital cataract or developmental cataract were defined according to the 11th Revision of the International Classification of Diseases (ICD-11) Beta Draft; 2) age 0-18y; and 3) informed, written consent provided by at least one guardian. Patients with recorded refraction measurements and more than two years of follow-up were included in the final analysis.

The exclusion criteria included the presence of any of the following 1) the presence of any other ocular comorbidities in the cataractous eye and/or the fellow eye, including and not restricted to history of corneal disorders, glaucoma, lens luxation, persistent hyperplastic primary vitreous and nanophthalmos, or systemic comorbidities (including but not restricted to Down syndrome, congenital rubella syndrome and juvenile idiopathic arthritis); and 2) cataracts secondary to other primary diseases, such as complicated cataracts (due to ophthalmic inflammation or degenerative changes), traumatic cataracts and metabolic cataracts.

Primary Data Collection Demographic information was obtained from each eligible patient, including gender, age, etiology, and laterality. The primary data collected also included the date of the surgery, the patient's age at the time of the surgery and the surgical strategy. All eyes of the subjects underwent a thorough ophthalmic evaluation, including slit-lamp biomicroscopy, fundus photography and B-scan ultrasonography.

Surgery Arrangement and Intraocular Lens Calculation All of the surgeries were performed by one of two experienced cataract surgeons (Liu YZ or Chen WR), and the surgical strategy was implemented according to the patient's age for all of the surgeries. Surgical cataract extraction with/without IOL implantation [lens irrigation/aspiration with posterior continuous curvilinear capsulorhexis and anterior vitrectomy (I/A+PCCC+A-Vit) for patients younger than 2y; or lens irrigation/aspiration with IOL implantation, posterior continuous curvilinear capsulorhexis and anterior vitrectomy (I/A+IOL+PCCC+A-Vit) for patients of 2-3y; lens irrigation/aspiration with IOL implantation (I/A+IOL+PCCC) for patients older than 3y] was performed in the included eye (refer to Table 1 for more details). The IOL power was calculated using the SRK-II formula[8]. The Acrysof SN60AT and MA60AC IOLs (Alcon Laboratories, Fort Worth, TX, USA) were used. The target postoperative refraction ranges from -2.0 to +4.0 D, depending on patient's age and the refractive status of the fellow eye[9]. Patch therapy was prescribed if the acuity difference between two eyes was higher than 0.70 logMAR. The detailed information on postoperative refraction correction was provided in Table 2.

Table 2 Postoperative refraction correction

Laterality	Treatment[a]	Postoperative refraction correction
Bilateral	Aphakia	Glasses
Unilateral	Aphakia	RGP lenses
Bilateral & unilateral	Pseudophakia	Bifocal glasses

RGP lenses: Rigid gas-permeable contact lenses. [a]<2y: +3.0 D overcorrection; ≥2y: +2.5 D overcorrection.

Follow-up of Participants and Refraction Measurement The protocol called for follow-up visits at 1wk, 1, and 3mo postoperatively (cataract removal and/or IOL implantation), then every 3mo in the first year, then every 6mo thereafter. Each follow-up visit required a complete eye examination which last about 3h including slit-lamp photography, tonometry, anterior segment analysis, and refractive error inspection. Autorefraction was performed with an un-dilated pupil. Objective retinoscopy was performed after dilating the pupil to evaluate refractive status. Compound tropicamide was used to dilate the pupil before examination. All refractions were performed by an experienced optometrist. Each patient might have more than one refractive result per year. The result that was taken about a year from his or her previous follow-up was included for analysis.

Definitions and Data Recording

Ocular refraction The refraction data from each follow-up visit were transformed and recorded as the spherical equivalent [SE; algebraic sum in diopters (D), sphere +1/2 cylinder].

Yearly myopic shift The yearly myopic shift (YMS) was calculated as the SE in the year$_{N+1}$ minus the SE in the year$_N$ in diopters.

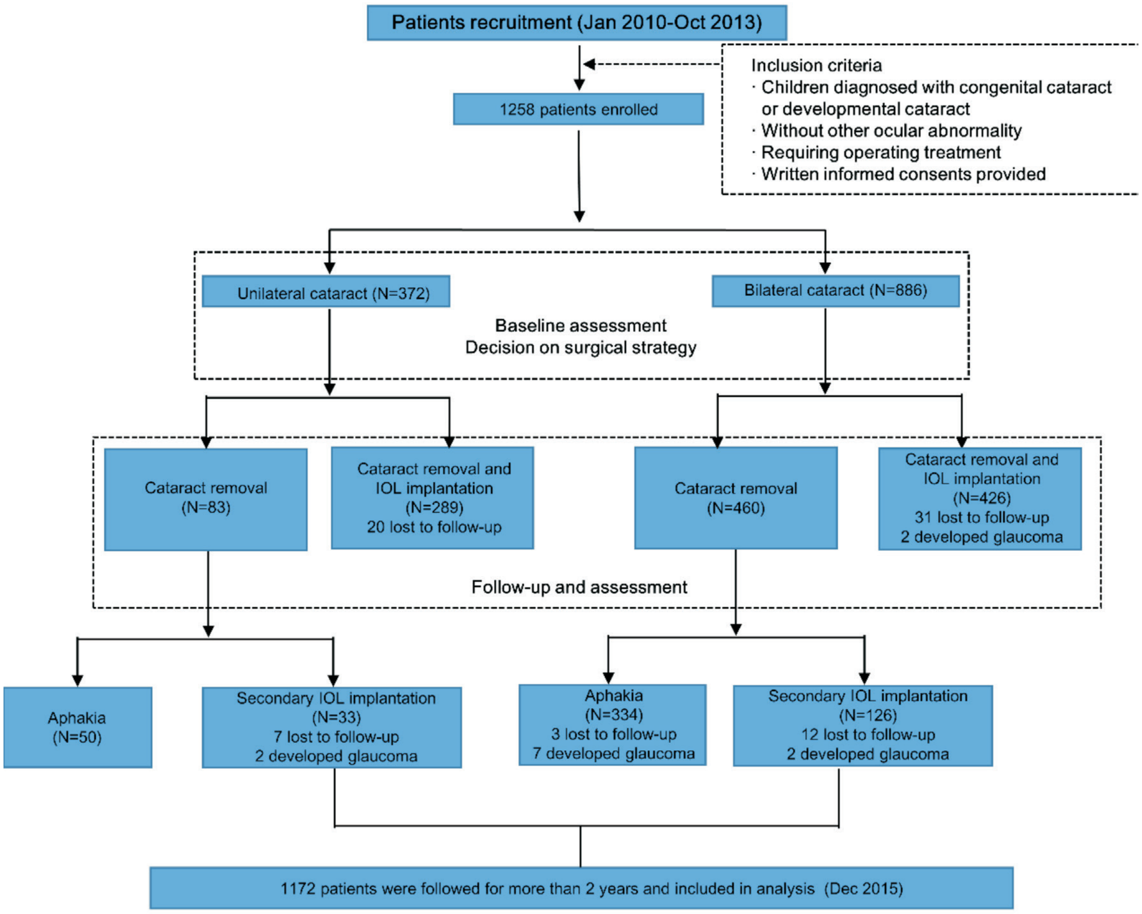

Figure 1 Pipeline detailing the enrollment of subjects in the study.

Non-affected eye The fellow eye without cataract in a patient with monocular cataract was defined as "healthy". In our study, fellow eyes were screened, and any ocular or systemic comorbidities were excluded (see the enrollment criteria). "Healthy" was only applied to the above-mentioned facets.

Statistical Analyses All of the statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA). The Shapiro-Wilk test was used to evaluate the normality of distribution for all variables. For variables fitting a normal distribution, data were recorded as the mean±standard deviation (SD). Otherwise, for variables not fitting a normal distribution, data were recorded as the medians and 25th-75th interquartile range. A linear mixed model (LMM) was used to analyze differences in SE with laterality, age, and gender in both aphakia and pseudophakia data separately. In the LMM, the ocular refractive SE that were repeatedly measured at different follow-ups were regard as independent variable, and postoperative time was included as a predictor. In addition, laterality (bilateral *vs* unilateral) and gender were included in LMM as fixed effects[10]. In this way, we were able to statistically control the influences of other factors when we looked at the effects on the refraction status caused either by age, laterality or gender. The "reference" in the LMM regression models referred to the category that was set as the reference level of a specific categorical variable. For example, gender is a categorical variable, and "female" was set as the reference level for gender. The AR (1) in LMM, which is a first-order autoregressive structure with heterogenous variances, is used to control the effects of repeated measurements of an individual. A paired *t*-test was used to evaluate the difference in SE between the affected eye and the fellow eye in unilateral PC patients. A two-tailed *P*-value <0.05 was considered statistically significant for all tests.

RESULTS

Baseline Characteristics A total of 1258 patients were enrolled, and 1172 (93%) were followed for more than two years and included in the statistical analysis (the pipeline of the procedures is shown in Figure 1). The median follow-up was 3y (interquartile range 2.5-4.5y). The ratio of bilateral cataract to unilateral cataract was 2.63:1 (829:343). Demographic information of the cohort is mentioned in detail in Table 3. The average number of records per individual is 4.49±1.43 records/child.

Ocular Refraction in Bilateral and Unilateral Aphakia There was no statistically significant difference in the age at surgery and the immediate postoperative refraction between unilateral aphakia and bilateral aphakia (Table 4). SE refractive error decreased with age in both bilateral and unilateral aphakic eyes (Figure 2). We found that SE refractive

Table 3 Demographic characteristics of the patients included in final analysis y, mean±SD

Treatment	Total		Male		Female	
	n	Age	*n*	Age	*n*	Age
Bilateral						
Aphakia	324	0.92±0.38	212	0.92±0.55	112	0.91±0.19
Primary IOL Implantation	393	6.06±2.99	246	5.94±3.97	147	6.26±2.52
Secondary IOL Implantation	112	2.89±0.82	76	2.85±0.62	36	2.98±0.36
Unilateral						
Aphakia	50	0.74±0.39	28	0.75±0.39	22	0.71±0.37
Primary IOL Implantation	249	4.80±3.37	146	5.01±3.70	103	4.49±2.85
Secondary IOL Implantation	24	2.35±0.54	16	2.35±0.56	8	2.38±0.46

For aphakia and primary IOL implantation, "Age" was referred to the age at enrollment. For secondary IOL implantation, "Age" was referred to the age when receiving IOL implantation.

Table 4 Comparison of ocular refraction and age at baseline in aphakia (*n*=510)

Variable	Unilateral	Bilateral	Statistics value	*P*
Age at surgery (y)	0.92 (0.83, 1.15)	0.92 (0.67, 1.58)	17299	0.271
Baseline SE (D)	16.48±2.78	16.77±2.99	-0.86	0.411

Using two independent sample *t* test for SE with *t* statistics, Wilcoxon rank sum test for age with W statistics. SE: Spherical equivalent.

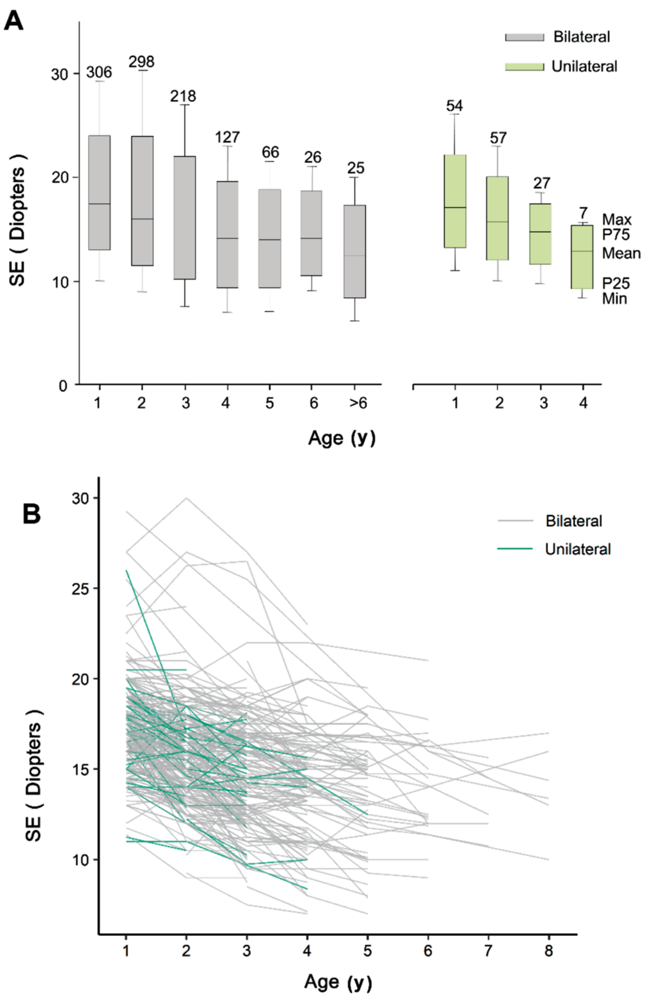

Figure 2 Ocular refraction in bilateral and unilateral aphakia with age A: The boxplot shows the SE in bilateral (grey) and unilateral (green) aphakia in each age group; B: The spaghetti plot shows the changing trend for SE of each bilateral (grey) and unilateral (green) patient in aphakia. SE decreases with age in bilateral and unilateral aphakic eyes.

error became myopic by 0.89 D yearly in aphakia after lens removal (*P*<0.0001). Males tended to have more myopic than females (*P*<0.0001). Factors that significantly affect the ocular refraction were gender, postoperative time and baseline ocular refraction (Table 5).

Ocular Refraction in Bilateral and Unilateral Pseudophakia There was significant difference in the age at surgery and the immediate postoperative refraction between unilateral pseudophakia and bilateral pseudophakia (Table 6). We further stratified the data of the immediate postoperative refraction according to the age of IOL implantation. There was no difference between unilateral pseudophakia and bilateral pseudophakia in most of the age range after stratification. We found significant difference in the patients younger than 2y and those older than 10y. However, it could not be concluded that the immediate postoperative refraction was different between unilateral pseudophakia and bilateral pseudophakia in these age ranges. The number of patients in some age group were too small, and we had to combine them for statistical analysis. The difference was likely due to the uneven distribution in age for these two age ranges.

SE refractive error decreased with age in both bilateral and unilateral pseudophakic eyes (Figure 3C). For bilateral PC patients, SEs in both eyes was similar for each age bracket. With the current strategy for IOL calculation, the SE refractive error for patients with bilateral pseudophakia showed a myopic shift with age and reached -0.49 to +0.49 D at approximately 6 years of age (Figure 3A). A similar profile of SE was observed in the affected eyes of the unilateral PC patients; the SE in the non-affected eyes of unilateral PC patients reached emmetropia at approximately 8-10y of age (Figure 3B). We

Table 5 Multivariate analyses of factors independently associated with ocular refraction in aphakia using LMM

Variable	Estimate	95%CI	SE	*t*-value	*P*-value
Age at surgery	-0.11	-0.57 to 0.34	0.23	-0.49	0.624
Gender					
Male	-0.75	0.29 to 1.21	0.23	3.20	<0.0001[a]
Female	Reference				
Laterality					
Unilateral	0.23	-0.55 to 1.03	0.40	0.60	0.552
Bilateral	Reference				
Postoperative time	-0.89	-1.03 to -0.74	0.07	-12.13	<0.0001[a]
Baseline ocular refraction	0.69	0.57 to 0.80	0.06	11.67	<0.0001[a]

LMM: Linear mixed model; CI: Confidence interval; SE: Standard error. "Reference" referred to the category that was set as the reference level of a specific categorical variable. [a]Statistically significant.

Table 6 Comparison of ocular refraction and age at baseline in pseudophakia (*n*=798)

Variable	Unilateral	Bilateral	Statistics value	*P*
Age at surgery	4.00 (2.90, 5.80)	4.90 (3.70, 6.80)	55088	<0.001[a]
Baseline SE	1.01±2.35	0.23±3.25	3.87	<0.001[a]

Using two independent sample *t* test for SE with *t* statistics, Wilcoxon rank sum test for age with W statistics. SE: Spherical equivalent. [a]Statistically significant.

Table 7 Multivariate analyses of factors independently associated with ocular refraction in pseudophakia using LMM

Variable	Estimate	95%CI	SE	*t*-value	*P*-value
Age at surgery	0.49	-0.21 to 0.30	0.13	0.38	0.704
Gender					
Male	-0.09	-0.44 to 0.26	0.18	-0.53	0.598
Female	Reference				
Laterality					
Unilateral	-0.47	-0.85 to -0.09	0.19	-2.49	0.013[a]
Bilateral	Reference				
Postoperative time	-0.43	-0.52 to -0.34	0.05	-9.40	<0.0001[a]
Baseline ocular refraction	0.72	0.63 to 0.81	0.04	16.11	<0.0001[a]

LMM: Linear mixed model; CI: Confidence interval; SE: Standard error. "Reference" referred to the category that was set as the reference level of a specific categorical variable. [a]Statistically significant.

further investigated the differences in SE between bilateral and unilateral PC pseudophakia using the linear mixed model (Table 7). SE decreased by 0.43 D yearly in pseudophakia after IOL implantation (*P*<0.0001). Laterality (bilateral *vs* unilateral) significantly affected the ocular SE in pseudophakic eyes (*P*=0.013).

To study differences in ocular refraction between pseudophakia and healthy eyes, data from the non-affected eyes of unilateral PC patients were introduced into a linear mixed model analysis (Table 8). The ocular refraction became myopic for both pseudophakic and phakic eyes. SE in pseudophakia was more myopic than that of healthy eyes (*P*=0.017). The paired *t*-test showed that the differences in SE between the affected eye and the fellow eye in unilateral PC was significant (*P*=0.0013).

Yearly Myopic Shift in Bilateral and Unilateral Pseudophakia The extent of YMS had a double-peak profile, one in young adulthood and another in early adolescence in pseudophakic and healthy eyes (Figure 4). In most of the age groups, the eye affected by PC showed a higher YMS, regardless of its laterality.

DISCUSSION

PC causes defocus and/or form deprivation during the critical period of ocular development; a PC patient who has an opaque lens removed requires optical correction of the resulting extensive hyperopia. Deciding on IOL power is a key step for optical rehabilitation for PC patients, and yet, is a long-lasting controversial issue. It is extremely difficult to predict when the refraction will stabilize for an individual patient. The postoperative refractive shift may vary from 0.52 to 36.3 diopters[9,11-13]. Furthermore, there is insufficient source data to fully characterize the dynamic refraction profile of PC patients to guide treatment strategy.

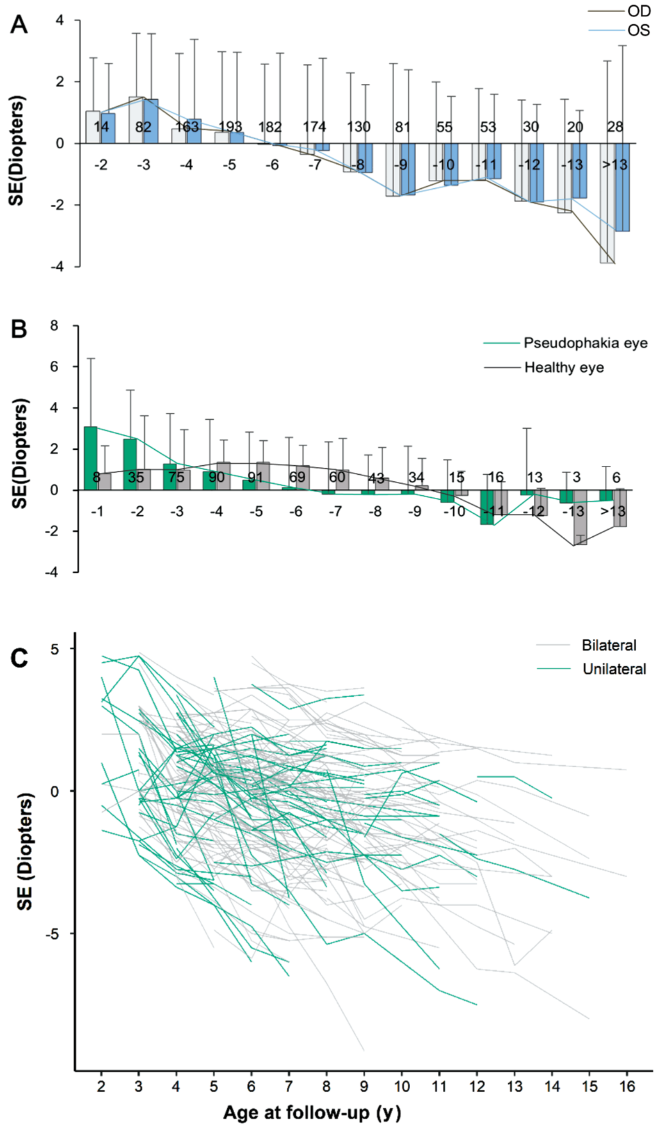

Figure 3 Ocular refraction in bilateral and unilateral pseudophakia with age The bar and line chart show the changing trend (mean) of SE in bilateral (A) and unilateral (B) pseudophakia. With the current strategy for IOL calculation, SE in bilateral pseudophakia becomes myopic with age and reached -0.49 to +0.49 D at approximately 6 years of age (A). A similar profile of SE is observed in the affected eyes in unilateral PCs; the SE in the non-affected eyes of unilateral PCs reaches emmetropia at approximately 8-10 years of age (B). C: The spaghetti plot shows the changing trend for SE of each bilateral (grey) and unilateral (green) pseudophakic patient, indicating that SE decreases with age.

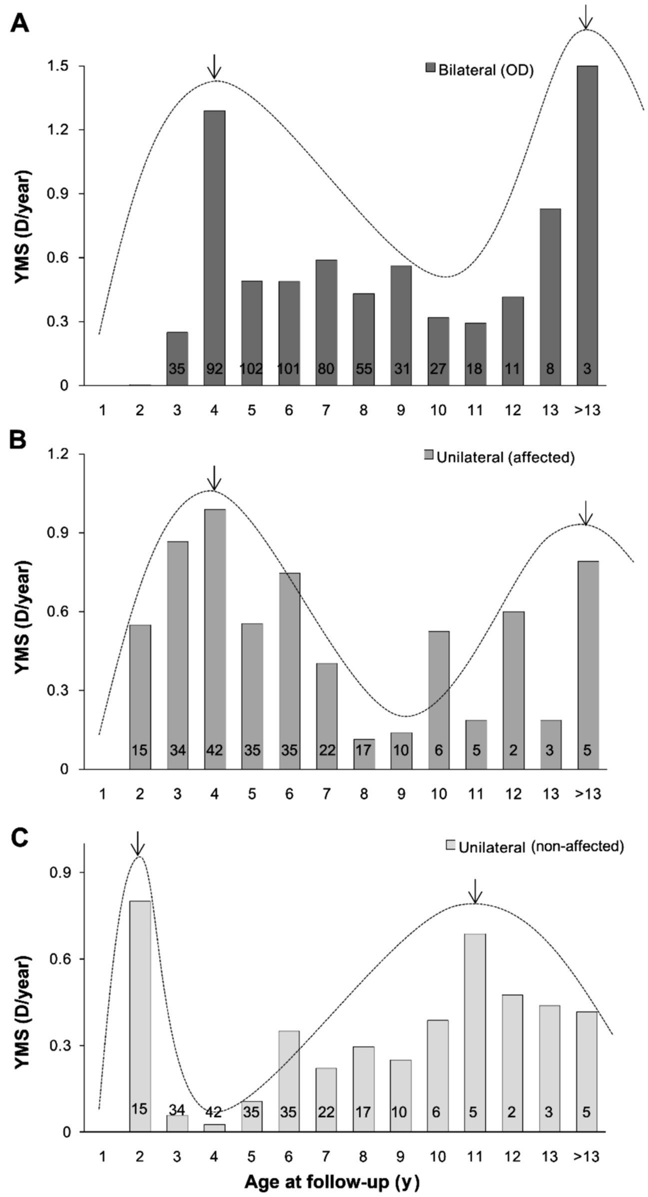

Figure 4 YMS in bilateral and unilateral pseudophakia and healthy eyes with age The bar chart shows the YMS in bilateral (A) and unilateral (B) pseudophakia, as well as in healthy eyes in patients with unilateral congenital cataract (C). Black arrows and the peak of the curve represent the peak of YMS. YMS is most fast in young childhood and early adolescence in pseudophakia and healthy eyes. In most age groups, the eye affected by PC shows a higher YMS, regardless of laterality.

In the current study, we prospectively recruited 1172 PC patients at one medical center, grouping and analyzing the changing refractive pattern of the subjects by laterality. In this longitudinal study with a large cohort, we observed some interesting results.

We used a linear mixture model to observe the effects of single factor on refractive changes while controlling other factors. The average refractive power became myopic by 0.89 D every year for aphakic eyes, and 0.43 D for pseudophakic eyes.

We found that among PC patients, the refractive pattern differed with gender in aphakic eyes. SE refractive error in males was more myopic than that in females. This is consistent with our previous study, in which we found that before cataract removal, the axial length of male PC patients was longer than that of females[14]. Furthermore, our result showed a difference between SE in unilateral of bilateral pseudophakia.

Data from our cohort demonstrated that the YMS grew the most rapidly in both young childhood (<3y) and early adolescence (>12y). Some studies have demonstrated that

Table 8 Multivariate analyses of factors independently associated with ocular refraction in pseudophakia and non-affected eyes using LMM

Variable	Estimate	95%CI	SE	*t*-value	*P*-value
Age at surgery	-0.12	-0.33 to 0.08	0.10		0.254
Gender					
Male	0.25	-0.05 to 0.56	0.15	1.61	0.109
Female	Reference				
Diagnosis					
Bilateral	-0.42	-0.76 to -0.08	0.17	-2.41	0.017[a]
Non-affected	Reference				
Postoperative time	-0.33	-0.42 to -0.24	0.05	-7.18	<0.0001[a]
Baseline ocular refraction	0.78	0.69 to 0.86	0.04	17.67	<0.0001[a]

LMM: Linear mixed model; CI: Confidence interval; SE: Standard error. “Reference” referred to the category that was set as the reference level of a specific categorical variable. [a]Statistically significant.

refraction changes rapidly in PC patients until the age of 1.5 to 3y and then stabilizes at the age of 8 to 10y, while other studies have found further myopic shift into early adolescence[1,9,15-16]. Currently the hyperopic range established for children at the time of IOL implantation is predicted according to the expected myopic shift in patients before 8 to 10y[1-2,9,17-18]. However, our data showed that in both cataractous and healthy eyes there is another rapid changing period of refraction during early adolescence. These results are consistent with the classical RRG serial studies, which demonstrated that the refraction development did not follow a simple linear pattern[3-6]. The double peak profile of the YMS illustrated that the ocular refraction became myopic fastest both during young childhood and early adolescence. That is why the refraction development could not be calculated with a linear equation. The rapid growth during early adolescence observed in our cohort may be a result of ethnic differences given the high rate of myopia seen in Asia[19-21]. In populations with a large risk of developing high myopia, strategies for IOL power determination may need to reflect these differences. The possible solutions for this phenomenon are to leave a larger hyperopic range after IOL implantation and/or to suppress the significant myopia shift through early post-operative overcorrection. This is the main focus of our further study in refractive development and IOL power determination of congenital cataract patients.

In most of the age groups, the YMS of PC eyes was relatively higher than that of healthy eyes, which could be partially explained by the fixed refractive power of the IOL that could not grow and compensate for the refractive change in the cornea as natural lens. Though a hyperopic range was established at the time of IOL implantation, eventually the pseudophakic eyes were more myopic than healthy contralateral eyes in our cohort.

In summary, our results support to set up target refraction basing on laterality of cataract involvement, age at IOL implantation and baseline ocular refraction. For those kindergarten patients, treatment of amblyopia is of priority, and the second peak of myopia shift is less important. For relative older patients who have better compliance with spectacle wearing and other treatments, we would like them to be 1 to 2 D myopic as adults so that they can have good uncorrected near acuity and reasonably clear uncorrected distance vision. We suggest postponing the age of IOL implantation to solve the dilemma of visual function development and more extensive myopic shift in our patients. This suggestion is consistent with a recent published study of 256 children with congenital or infantile cataract[22]. The prerequisite was proper refraction correction under ophthalmologists’ instructions. Our recommendations for target refractions based on the results of our cohort are presented in Table 9.

The results and interpretation of the current study must be understood within the context of its strengths and limitations. In our cohort, some binocular patients underwent a secondary IOL implantation at an older age compared to monocular patients. The late surgical time brings possible influences on the refractive outcome of unilateral and bilateral patients. Although patients were referred to the hospital from all parts of China, all the subjects were treated and followed at one medical center. The results may not be representative for other cohorts. Although we used the linear mixed model to adjust for confounding factors, the use of non-affected eyes of patients with unilateral PC as a “healthy” control possesses potential influences on the results[23].

Despite these limitations, the results of our study confirm critical factors, such as baseline ocular refraction and post-operative time, contributing to the refractive outcome in PC patients. What is more, further concerns should be raising to monitor the rapid myopic shift at early adolescence of these patients.

Table 9 Recommended strategies and target refractions

Conditions (y)	Strategies and target refractions
Bilateral	
<2	IOL implantation not recommended
2-5	Spectacles correction recommended; IOL implantation: refer to Enyedi *et al*[9]
5-8	+4, +3, +2, +1 D
Unilateral	
<2	IOL implantation not recommended
2-5	RGP correction recommended; IOL implantation: refer to Enyedi *et al*[9]
5-8	2-3 D hyperopia than the non-affected eye
Baseline spherical equivalent of ocular refraction: more hyperopic than (28-3×age) D	The reserved hyperopia should be 1 D more than that of the above-mentioned target refractions.

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