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Original Research

Practical pattern of surgical timing of childhood cataract in China: A cross-sectional database study

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ABSTRACT

Background: The ideal surgical timings for cataract extraction (CE) and intraocular lens (IOL) implantation are vital for vision reconstruction in patients with childhood cataract (CC), yet they still remain controversial. We aimed to analyze the real-world practical pattern of surgical timings of CE and IOL implantations among a large number of Chinese CC patients.

Materials and methods: This cross-sectional, database study included CC inpatients from the *** over a 10-year period (from January 2005 to December 2014). Binary logistic regression and multiple linear regression analyses were performed to identify the factors affecting the timings of CE and IOL implantation.

Results: In the primary surgical stage, the mean ages of patients performed with CE ($n = 839$) and CE + IOL implantation ($n = 1582$) were 9.99 ± 18.21 months (5^{th}-95^{th} percentiles: 2–21) and 82.99 ± 52.99 months (5^{th}-95^{th} percentiles: 24–194), respectively. Surgical age, laterality, and axial length were identified as three factors (area under the curve [AUC]: 0.96, 95% CI: 0.94–0.97; Youden index: 0.86) affecting surgical procedure selection (CE or CE + IOL implantation) in the primary surgical stage. The time intervals between primary CE and secondary IOL implantation in bilateral ($n = 311$) and unilateral ($n = 90$) aphakia were 38.25 ± 16.84 months (5^{th}-95^{th} percentiles: 18–72) and 25.87 ± 10.56 months (5^{th}-95^{th} percentiles: 11–48), with significant difference ($p < 0.001$). Age at primary CE and laterality were identified as two factors affecting the time interval between primary CE and secondary IOL implantation in aphakic patients.

Conclusions: The timings of CE and IOL implantation mainly varied with the age and laterality. This study may provide data-based clinical experience for ophthalmologists regarding CE and IOL implantation of CC in China and other countries with similar socioeconomic conditions.

1. Introduction

Randomized controlled trials (RCTs) are generally considered the gold standard for evaluating the safety and efficacy of clinical treatments within restricted trial settings [1]. However, the validity of RCTs relies on narrow and restricted patient populations after the application of extensive inclusion and exclusion criteria to a considerable number of cases [2], which may limit the generalizability of RCTs to the clinical treatment of rare diseases with a limited number of widely dispersed patients [3]. Childhood cataract (CC) is a rare condition with a prevalence of only 4.24/10000 [4], but it is the leading cause of childhood blindness in many areas of the world [5]. Surgery is the only effective treatment for most CC patients [6]. Scientists and ophthalmologists have directed extensive efforts toward the development of appropriate surgical treatment strategies for CC. The experience from the Infant Aphakia Treatment Study (IATS), a multicenter [12], randomized, controlled clinical trial including 114 unilateral CC infants [7] in the USA, is regarded as a guide for determining whether CC patients should be considered for intraocular lens (IOL) implantation [6]. However, some medical questions such as surgical timings cannot be answered by the study design of RCT. Furthermore, due to the limited number of cases and multiple influential factors, conducting RCTs with larger sample sizes for CC treatment worldwide is extremely challenging. Currently, the ideal timings for cataract extraction (CE) and IOL implantation remain controversial [8,9], which are vital for the restoration of clear dioptric media and the improvement of visual acuity in CC

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patients.

Real-world data (RWD) are from databases and patient medical chart reviews and registries [1] rather than obtained from conventional RCTs [10]. The use of RWD is increasingly recognized as a valuable strategy for making surgical decisions in the treatment of rare diseases [1,3,11]. Clinical RWD-based practice pattern has been recommended in CC management to optimize surgical strategies for CC patients [12]. In the current study, we analyzed the surgical RWD of 2421 CC children from the *** (CCPMOH) [13] at the *** and proposed data-based clinical experience for the timings of CE and IOL implantation. This study not only provides a practical experience regarding CC treatment for ophthalmologists but also demonstrates an approach for determining treatment strategies for other rare diseases.

2. Methods and materials

2.1. Patients and ethics statement

We conducted a clinical real-world database study of the hospital charts of CC patients over a 10-year period (from 1 January 2005 to 31 December 2014) from CCPMOH in China. Most newly diagnosed CC patients were directly or referred to and registered in CCPMOH from the general or eye hospitals among 28 provinces (28/34, 82.35% of a total of 34 Chinese provinces) all over China [13,14]. CCPMOH is an organization with the largest clinical database of CC aimed at the prevention and treatment of childhood cataract in China and was established by Ministry of Public Health of China. In the database of the Medical Records Department of CCPMOH at the ***, which encodes cataract types and ocular abnormalities using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The patients were anonymized and CC hospitalizations were identified from the following three codes: congenital cataract and lens anomalies (743.3), infantile cataract (366.0), and aphakia and other disorders of the lens (379.3). All CC patients treated surgically for the first time at the age of ≤18 years were included. Drug-induced cataracts, traumatic cataracts, metabolic cataracts, secondary cataracts, and cataracts complicated with lens luxation were excluded. Written informed consent was obtained from the legal guardian of each registered patient in CCPMOH during registration. The work has been reported in line with the STROCSS criteria [38].

2.2. Information extraction

The flow chart of this study is shown in Fig. 1. In the first surgical stage, a subset of CC patients (Group 1) received CE without IOL implantation, whereas the others (Group 2) received CE and primary IOL implantation. To determine the factors affecting the selection of surgical procedures in the first stage, the surgical age, gender, laterality, and axial length (AL) of the CC patients were extracted and compared between groups. To determine the time interval between primary CE and secondary IOL implantation, the age at secondary IOL implantation (the second surgical stage) in Group 1 was also tracked. The time interval was calculated by subtracting the two surgical ages: age at secondary IOL implantation − age at primary CE. Gender, laterality, age, and AL at the second surgical stage among CC patients in Group 1 were also considered as affecting factors in determining the timing for secondary IOL implantation. All eligible data were carefully reviewed by two independent researchers (*** and ***).

2.3. Mathematical modeling and statistical analysis

The data were input into Microsoft Excel (ver. 2013, Microsoft Corp., Redmond, WA, USA) spreadsheets and were sorted and mutually reviewed by two researchers (*** and ***). Then, the data were analyzed with the Statistical Package for the Social Sciences (SPSS ver. 19.0, Chicago, IL, USA). The 5th and 95th percentiles were used to

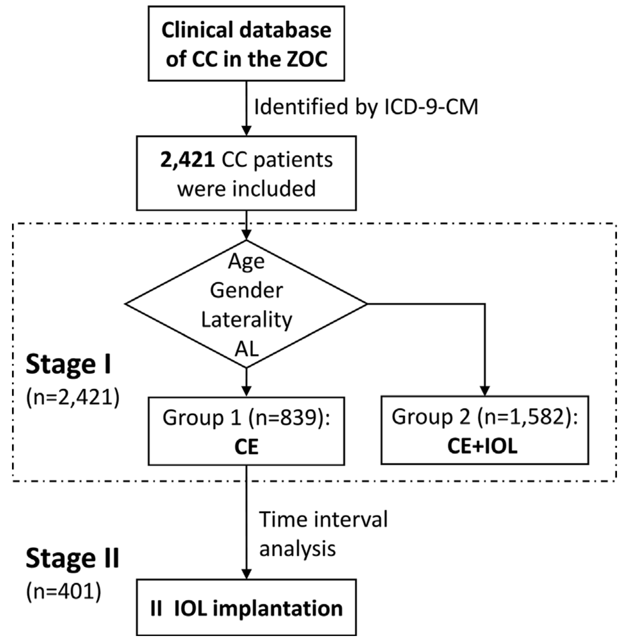

Fig. 1. Flow chart of the study design. In the first surgical stage, the age, gender, laterality, and AL of the patients were analyzed as possible factors affecting surgical procedure selection (CE or CE + IOL). In the second surgical stage, the factors affecting surgical procedure selection and the time interval between primary CE and secondary IOL implantation were analyzed. CC: childhood cataract; AL: axial length; CE: cataract extraction; CE + IOL: cataract extraction and primary IOL implantation; II IOL implantation: secondary IOL implantation; Stage I: the first surgical stage; Stage II: the second surgical stage.

exclude outliers in the age and AL dataset [15]. Comparisons of surgical age, gender, laterality, and AL between the two groups were performed using independent-samples t tests. The time interval between primary CE and secondary IOL implantation among the Group 1 patients was calculated with Microsoft Excel using the formula [= datedif (start_date, end_date, “unit”)] (notes: start_date, age at CE; end_date, age at secondary IOL implantation; unit, month, or year). Binary logistic regression (BLR) was performed to identify the factors affecting surgical procedure selection in the first surgical stage and to establish a mathematical model for estimating whether the CC patients should be primarily implanted with IOLs in the first surgical stage. The calibration of the model was validated using the Hosmer-Lemeshow test [T= $\sum_{i=1}^{k}\left((O_i - E_i)^2/\left(\frac{E_i x E_i}{n_i}\right)\right) \sim x_{k-2}^2$] [16]. The discriminatory capacity of the model was assessed by the area under the curve (AUC) and the Youden index. Multiple linear regression (MLR) analysis was performed to identify the factors affecting the timing of secondary IOL implantation in the second surgical stage and to establish a mathematical model for predicting the timing of secondary IOL implantation in aphakic patients. The level of significance in this study was set to $p < 0.05$.

2.4. Treatment effects analysis

To determine the treatment effects of the models of the surgical timing of CC in the ***, 150 CC patients (100 bilateral and 50 unilateral) with at least 3 years of follow-up were randomly selected from the database of the CCPMOH [14] and analyzed. The 150 patients were selected based on the following procedures. Firstly, 1223 CC patients with a follow-up period ≥3 years were identified and divided into two groups: bilateral patients (N = 771) and unilateral patients (N = 452). Secondly, the bilateral patients were labeled from 1 to 771. Then 100 numbers between 1 and 771 were generated by an online Random Number Generator and the 100 bilateral patients with the same number labels were picked out. Fifty unilateral patients were also randomly selected in the same way.

Besides routing CE and IOL implantation, posterior continuous curvilinear capsulorhexis (PCCC) and anterior vitrectomy were performed in CC patients younger than 6 years old at the times of surgery. All CC patients in the CCPMOH were followed up according to the following time points: 1 week, 1 month, 3 months, 6 months after surgery, and every half-year thereafter. The primary outcome was the final visual acuity (best corrected visual acuity, BCVA) at the last follow-up. The secondary outcomes were the rates of ocular hypertension (OH, > 21 mmHg, or glaucoma), treatment with yttrium-aluminum-garnet (YAG) laser capsulotomy (for visual axial opacity, VAO), and revision surgeries within 1 year after surgery. The ocular pressure was measured by a noncontact tonometer (TX-F, Canon, Tokyo, Japan), and the VAO was evaluated by a slit-lamp (BX900, HAAG-STREIT, Switzerland). The data regarding information on follow-up visits, visual acuity, ocular pressure, and other postoperative treatments mentioned above were obtained from records. The treatment effects of the 150 patients were compared with those reported in studies published within the last 5 years (2013–2017).

3. Results

During the study period, a total of 3759 patients were screened as eligible on the basis of ICD. Five hundred and fifteen patients were excluded for older than 18 years old and 823 patients with other type cataracts were also excluded. A total of 2421 CC patients were finally included, 66.25% (1604/2421) of whom had bilateral involvement, and the ratio of males to females was 1.56 (1477:944).

3.1. The first surgical stage

In the first surgical stage, 65.34% (1582/2421) of the CC patients received CE and primary IOL implantations, and the remaining were subjected to CE surgeries without IOL implantations. A comparison of the characteristics of the patients is shown in Table 1. The ages, ALs, and ratios of gender and laterality between the two groups were significantly different. The BLR analysis identified age, laterality, and AL as three factors affecting the selection of surgical procedures (CE or CE + IOL) among CC patients in the first surgical stage (Table 2).

3.2. Secondary IOL implantation stage

Overall, 401 patients who underwent CE in the first surgical stage and had relatively complete information for secondary IOL implantation in the second surgical stage were further analyzed. Due to the variation in ocular development between bilateral and unilateral patients, the ages and ALs of CC patients with different laterality were also

Table 1
Comparison of the ages, ALs, and ratios of gender and laterality between patients who received two different surgical procedures in the first surgical stage.

	CE	CE + IOL	χ^2/t	P
Number (%)	839 (34.66)	1582 (65.34)	–	–
Males/Females	548/291	929/653	10.017	0.002#
Bilateral/ Unilateral	676/163	928/654	117.736	< 0.001#
Age (months) (5th-95th percentiles)	9.99 ± 18.21 (2–21)	82.99 ± 52.99 (24–194)	49.553	< 0.001*
Axial Length (mm) (5th −95th percentiles)	19.82 ± 1.66 (16.99–22.27)	22.94 ± 2.11 (20.25–27.79)	17.518	< 0.001*

Notes: CE: cataract extraction; CE + IOL: cataract extraction and primary intraocular lens implantation; mm: millimeters; #(Chi-square test) and *(Independent *t*-test): $p < 0.05$, significant difference.

Table 2
Binary logistic regression analysis for the factors affecting surgical procedure selection in the first surgical stage.

Variable	B	OR	OR (95%CI)	P
Gender	−0.089	0.915	0.610–1.372	0.666
Age	0.628	1.873	1.244–2.822	0.003*
Laterality	−0.097	0.908	0.895–0.921	< 0.001*
AL	−0.318	0.727	0.643–0.822	< 0.001*

Notes: AL: axial length; *: $p < 0.05$, significant difference.

compared in the second stage. The distributions of the age at secondary IOL implantation and the time interval between primary CE and secondary IOL implantation are shown in Fig. 2. Detailed information regarding the time interval and the increase in AL between the two surgical stages are presented in Table 3. The mean surgical age of the bilateral patients at the first stage was 7.02 ± 5.02 months, which was younger than that of the unilateral patients (8.54 ± 5.79 months). However, the mean age at secondary IOL implantation of the bilateral patients was older than that of the patients with unilateral involvement (45.26 ± 16.97 vs. 34.40 ± 10.98 months, $p < 0.001$). The time intervals between primary CE and secondary IOL implantation in the bilateral and unilateral CC patients were 38.25 ± 16.84 and 25.87 ± 10.56 months, respectively ($p < 0.001$). Moreover, MLR analysis identified laterality and the age at primary CE as two factors affecting the time interval between the two surgical stages (Table 4).

3.3. Factors affecting the timings of primary CE and secondary IOL implantations

First surgical stage: A stepwise BLR analysis was performed, using age, laterality, and AL as relevant factors affecting the selection of surgical procedures in the first surgical stage. The estimation model was calibrated appropriately and could discriminate between CE and CE + primary IOL implantation very well (AUC: 0.96; 95% confidence interval [CI]: 0.94–0.97; Youden index: 0.86).

$$\text{Logit}(P) = 7.929 - 0.096{*}\text{Age} + 0.612{*}\text{Laterality} - 0.317{*}\text{AL} \quad (1)$$

Notes: Age in months; Laterality: 1 in bilateral and 0 in unilateral; AL: axial length in mm; Logit $(P) \geq 0.5$ suggests cataract extraction; Logit $(P) < 0.5$ suggests cataract extraction + primary IOL implantation.

Secondary IOL implantation stage: A model calculating the time interval between primary CE and secondary IOL implantation based on the MLR analysis was constructed. Laterality and age at primary CE were two factors considered in the mathematical model, and the following prediction model was constructed:

$$Y = 29.271 - 0.399{*}\text{Age} + 11.772{*}\text{Laterality} \ (\text{adjusted } R^2 = 0.11, p < 0.001) \quad (2)$$

Notes: Y: the time interval between primary cataract extraction and secondary IOL implantation; Age in months; Laterality: 1 in bilateral and 0 in unilateral.

3.4. Treatment effects on children with CC based on the surgical treatment mode at the ***

The ratio of males to females among the 150 randomly selected patients was 77:73, and the mean follow-up was 44.50 ± 23.95 months. The BCVAs at the last follow-up were better than the mean values reported in other studies, as summarized in a review study [17], with respective values of 0.27 vs. 0.57 (log MAR) in bilateral patients and 0.74 vs. 0.9 in unilateral patients. The rates of postoperative complications were as follows: ocular hypertension (15.33%, 23/150), YAG treatment for severe VAO (15.33%, 23/150), and re-surgery (0.67%, 1/150). The detailed information of these patients and

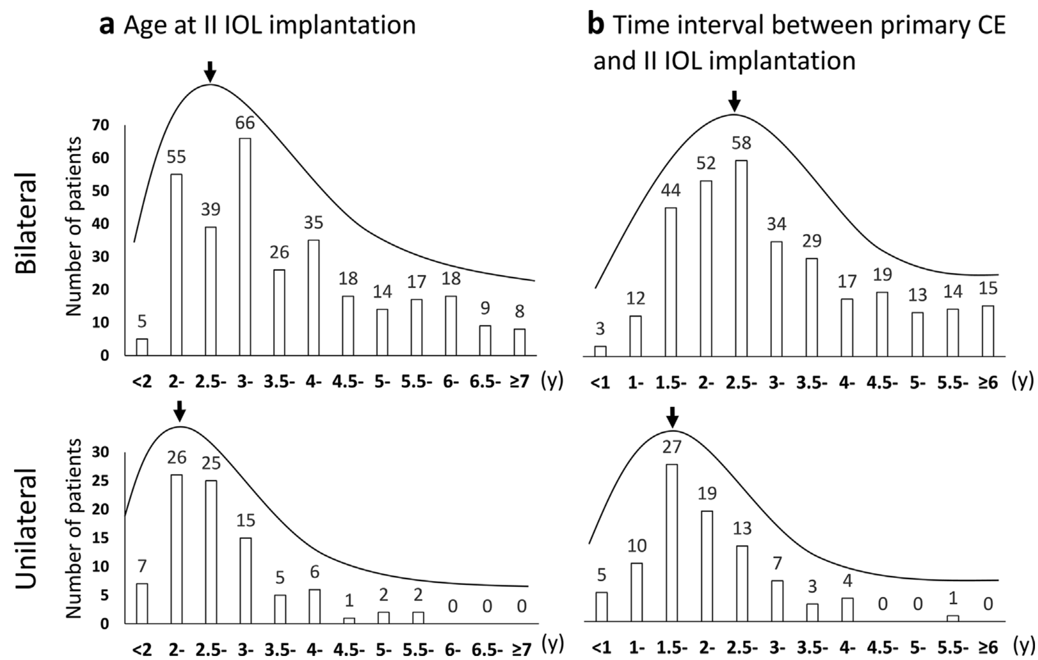

Fig. 2. Distributions of age at secondary IOL implantation (a) and the time interval between primary CE and secondary IOL implantation (b). Black arrow: peak age/time interval of II IOL implantation; CE: cataract extraction; II IOL implantation: secondary intraocular lens implantation; y: years.

Table 3
Ages and ALs of CC patients between primary CE and secondary IOL implantation.

	N	Age - I (m) (5th-95th percentiles)	Age - II (m) (5th-95th percentiles)	△ Time (m) (5th-95th percentiles)	AL-I (mm) (5th-95th percentiles)	AL-II (mm) (5th-95th percentiles)	△ Length (mm) (5th-95th percentiles)
Bilateral	312	7.02 ± 5.02 (2–18)	45.26 ± 16.97 (25–78)	38.25 ± 16.84 (17.6–71.5)	19.60 ± 1.76 (16.9–22.9)	22.18 ± 1.89 (19.3–25.5)	2.73 ± 1.43 (0.68–5.37)
Unilateral	89	8.54 ± 5.79 (3–18)	34.40 ± 10.98 (20.5–58.5)	25.87 ± 10.56 (11–48)	20.36 ± 1.15 (17.9–22.1)	22.12 ± 1.67 (18.9–25.0)	2.33 ± 1.33 (0.18–4.60)
t	–	−2.435	5.699	6.571	−2.770	0.247	1.343
p	–	0.015*	< 0.001*	< 0.001*	0.007*	0.805	0.182

Notes: Age - I: the age at primary cataract extraction; Age - II: the age at secondary IOL implantation; AL: axial lengths; m: months; mm: millimeters; *: Independent *t*-test, $p < 0.05$, significant difference.

Table 4
Multiple linear regression analysis for the factors affecting the time interval between primary cataract extraction and secondary IOL implantation.

Variable	B	OR (95%CI)	Standard B	p
Age	−0.399	-(0.694–0.104)	−0.127	0.008*
Gender	−0.089	0.610–1.372	0.915	0.666
Laterality	−0.097	0.895–0.921	0.908	< 0.001*

Notes: Age: age at primary cataract extraction; *: Independent *t*-test, $p < 0.05$, significant difference.

comparisons with other studies are presented in Supplementary Table A1.

4. Discussion

The prevalence of CC in developing countries is approximately 10 times higher than that in developed countries [18]. Exploring special treatment modes for CC patients living in developing areas is vital. In this study, we analyzed the surgical RWD of 2421 CC patients and identified the factors affecting the timings of CE and IOL implantation. Surgical age, laterality, and axial length were identified as three factors affecting surgical procedure selection (CE or CE + IOL implantation) in the primary surgical stage. In the secondary IOL implantation stage, the IOL implantation is recommended approximately 2 and 3 years after CE in unilateral and bilateral aphakic patients, respectively. Age at primary CE and laterality were identified as two factors affecting the time interval between primary CE and secondary IOL implantation in aphakic patients. This clinical RWD study maximizes the use of limited medical data of CC collected under real-life conditions which may provide a new approach for developing treatment strategies for rare diseases.

The mean age at primary CE among CC patients in this study was 57.69 months, which was similar to the findings of other developing countries, including 65 months in Iran [19], 88.8 months in Paraguay [20], and 55.2 months in India [21]. The suggested ages for CE for visually significant unilateral and bilateral congenital cataracts were 4–6 weeks and < 8 weeks, respectively [9]. In most developed countries, CC patients can be identified within 100 days [22]. The variation in surgical age between developing and developed countries may be due to differences in national screening policies for CC [22,23], the technical and diagnostic capacities of hospitals, and the health consciousness of patients. Early CE is recommended to preserve patients' vision once visually significant cataracts are detected, but the decision should be balanced against the risks of developing secondary glaucoma [24] and exposing children to general anesthesia during a key period of neurodevelopment [25]. For these reasons, nearly all CC patients in the *** received primary CE at an age older than 2 months.

Compared with the consensus for CE, the minimum age for primary IOL implantation remains controversial [9]. Primary IOL was performed in most CC patients during the first year of life in Sweden and

Denmark [26]. In France, CC patients with primary IOL implantation at a median age of only 5.7 months also achieve satisfactory visual outcomes [27]. However, most studies have reported that IOLs are not routinely implanted in infants younger than 6 months old but are always performed in children at least 2 years old [6]. Our study identified age, laterality, and AL as three factors affecting the decision over whether IOL implantation was performed in a primary CE surgery. Of these, age was found to be a major influential factor in surgical decision-making, and IOLs were implanted along with primary CE in more than 95% of CC patients who were older than 2 years of age. Collectively, primary IOL implantation should be avoided in CC infants younger than 2 years. First, the implantation of IOLs in very young patients usually increases the risks of postoperative complications and additional surgeries [28]. Second, most IOLs are sized for adults. Unmatched adult-sized IOLs and the immature lens bag of CC infants may result in complications. For example, we observed that severe deformation of both the anterior and posterior capsulorhexis of the lens bag (from a circle to an ellipse) was observed after implanting an adult-sized IOL in nearly 30% of young patients (Supplementary Fig. A1), which could lead to IOL dislocation or decentration. The high refraction prediction error may be another factor to consider [29] due to the irregularity of eyeball development [30,31], the difficulty in attaining IOL parameters in awake patients [6], and the lack of an accurate IOL calculation formula for pediatric CC patients [32]. Furthermore, frame glasses or contact lenses can usually achieve satisfactory refractive correction and may be a better choice for young aphakic patients during the period between primary CE and secondary IOL implantation [33].

In addition to surgical techniques, the socioeconomic status and environmental circumstances of the population should also be considered when determining the timing of primary IOL implantation in developing countries. An intensive follow-up is required after primary IOL implantation due to the high risk of postoperative complications in very young patients [8], which is very difficult for CC families living in remote areas and for those with limited education and income.

The optimal timing for secondary IOL implantation for aphakia should balance the risk of postoperative myopic shift, the timely refractive correction of IOLs, and the danger of repeated exposure to general anesthesia within a short period in young children [34]. Knowing the general age at which secondary IOL implantation is recommended will also help parents, particularly those in developing areas, prepare for mental and financial burdens. Our study revealed that laterality was the major concern for the timing of secondary IOL implantation. In bilateral cases, aphakic patients had IOLs implanted at 45.26 months of age and approximately 3 years after primary CE. IOLs were implanted in unilateral aphakic patients at 34.40 months of age and approximately 2 years after primary CE to reduce the risk of amblyopia caused by binocular competition. These results were similar to the findings reported in east China by Rong et al. [35] in 2015. Wood et al. [36] also reported a mean age of 55.2 ± 21.6 months at secondary implantation in 49 patients in the USA. In this study, most aphakic patients had IOLs implanted before 6.5 years of age. In China, 6–7 years is the age at which children begin primary school. Children with CC are not supervised by parents in schools and usually have poor compliance with wearing frame glasses with thick lenses. Furthermore, school-age children play with each other, and wearing a pair of "heavy" frame glasses may be inconvenient [37].

This study has limitations. First, although satisfactory treatment effects of this clinical pattern were preliminarily evaluated by 150 randomly selected patients, more clinical evidence will be added in our following prospective and comparative studies. Second, the experience of surgical timing was proposed based on the clinical RWD of a representative Chinese CC population; however, racial differences in ocular development [30] and socioeconomic disparities between Eastern and Western countries may limit the generalizability of the study's findings to other areas. Moreover, national policies, medical conditions, levels of education, and the economic health of CC families also vary from country to country. Therefore, each country is encouraged to use its own clinical RWD to establish a practical surgical schedule for CC treatment according to the country's actual circumstances. Nevertheless, we took the first step in using these RWD to propose a clinical experience for the surgical timings in patients with CC, which provided pediatric ophthalmologists with clinical refence for the surgical procedure selection in the first surgical stage and the timing of secondary IOL implantation. This database study may also serve as an important supplement to RCTs for the development of treatment strategies for rare diseases in general.

5. Conclusion

The timings of CE and IOL implantation mainly varied with the age and laterality. This study may provide data-based clinical experience for ophthalmologists regarding CE and IOL implantation of CC in China and other countries with similar socioeconomic conditions.

Ethical approval

This study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Zhongshan Ophthalmic Center at Sun Yat-sen University (IRB-ZOC-SYSU).

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Conflicts of interest

No conflicting relationship exists for any author.

Research registration number

We have already registered at Clinicaltrials.gov. UIN number is NCT03640780.

Guarantor

Haotian Lin, Weirong Chen and Duoru Lin agree to be accountable for all aspects of the work.

Data statement

Due to the protection of patient privacy in this study, the demographic information and surgical data would remain confidential and would not be shared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Duoru Lin: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing - review & editing. **Zhenzhen Liu:** Data curation, Methodology, Validation. **Jingjing Chen:** Data curation. **Zhuoling Lin:** Data curation. **Yi Zhu:** Writing - review & editing. **Chuan Chen:** Writing - review & editing. **Mingxing Wu:** Data curation. **Haotian Lin:** Conceptualization, Writing - review & editing, Funding acquisition. **Weirong Chen:** Conceptualization, Funding acquisition. **Yizhi Liu:** Conceptualization, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.01.012.

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