A Model to Predict Postoperative Axial Length in Children Undergoing Bilateral Cataract Surgery With Primary Intraocular Lens Implantation

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• PURPOSE: **To develop a model for predicting postoperative globe axial length (AL) in children undergoing bilateral cataract surgery with primary intraocular lens (IOL) implantation in children older than 2 years.**

• DESIGN: **Retrospective case series.**

• METHODS: **Children were included only if AL data were available for both eyes before surgery and at least 1 year after surgery. We analyzed variables that could influence globe axial growth and developed a multivariable generalized estimating equation regression model to predict postoperative AL.**

• RESULTS: **Sixty-four children were included. The median age at surgery and at follow-up was 5.1 and 12.5 years, respectively. AL measurements were obtained in both eyes during 242 visits. The median AL before and at last follow-up was 22.2 and 23.1 mm, respectively. Beta value for the final model to predict postoperative AL is as below: intercept (1.93), preoperative AL (0.91), age at cataract surgery (–0.07), age at follow-up (0.14), and interaction between age at surgery and age at follow-up (–0.005). Using this model, for a hypothetical patient operated at 2.5 years of age with a 20.5 mm AL would be estimated to have a 22.8 mm AL at 18 years of age.**

• CONCLUSION: **IOL power selection is a major challenge of pediatric cataract surgery attributable to unpredictable future eye growth. This model theoretically could be used to predict individual future adult size AL for each child undergoing cataract surgery, helping the surgeon to customize the selection of an IOL power at implantation and also to help the parents understand what to expect. (Am J Ophthalmol 2019;206: 228–234. © 2019 Elsevier Inc. All rights reserved.)**

Globe axial length (AL) is the most important measurement in determining the power of an intraocular lens (IOL) to be implanted for the correction of residual aphakia after cataract surgery. However, choosing the best IOL power for children is complicated by the fact that AL is still changing and eye growth is highly variable and can be difficult to predict. If a model could be developed to better understand and predict the axial growth of individual eyes after cataract surgery, pediatric surgeons could better customize the selection of an IOL power for each patient and it would also help parents to understand what to expect. More than 20 years ago, a computer program was published that predicted pseudophakic refraction versus age, allowing the surgeon to dynamically view the effects of changing the IOL power.[1] Herein, we aim to develop a new model that will predict postoperative AL in eyes of children undergoing cataract surgery. This may allow the surgeon to calculate IOL power using a predicted future AL or select undercorrection based on age and AL rather than determining the IOL power using only age-directed nomogram.

Currently while selecting IOL power, the surgeon usually chooses an undercorrection based on the age at surgery. However, AL is variable and AL growth is even more variable, but we have not been taking these individual differences into account at the time of cataract surgery. For example, if two 3-year-old children are scheduled for bilateral cataract surgery—one with an AL of 21.95 mm (average taken from published data of pediatric cataract[2]) and another with an AL of 20.34 mm (average minus 1 standard deviation from published data on biometry of pediatric cataract,[2]) both would be typically undercorrected by 3 diopters (D), to allow for future eye growth and myopic shift of refraction without factoring in the patient's preoperative AL. We will discuss below how predicting AL would help selecting IOL power for the above 2 patients. We propose to incorporate AL in addition to age at cataract surgery when deciding how much to undercorrect at the time of IOL implantation. The goal is to better predict, for individual patients, the IOL power needed to achieve emmetropia at age 20 years.

To help achieve this goal, we aimed to develop a model to predict future AL in children having bilateral cataract surgery with primary IOL implantation above two years of age, with the goal of optimizing IOL power selection. Because AL growth in infancy is more variable,[2] we focused this study on surgery performed after 2 years of age, when growth is relatively slower and slightly more predictable. Furthermore, a primary IOL is implanted more frequently in children undergoing cataract surgery after 2 years of age.

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METHODS

THIS STUDY RECEIVED EXEMPT STATUS FROM THE INSTITUTIONAL Review Board of the Medical University of South Carolina. The charts of pediatric patients who underwent bilateral cataract surgery with primary IOL implantation at the Storm Eye Institute were retrospectively reviewed. We included patients who had cataract surgery with primary IOL implantation in both eyes after 24 months of age with baseline AL measurements taken before surgery and with at least 1-year follow-up AL measurement taken after surgery in both eyes. Patients with traumatic cataracts, ectopic lentis, and preoperative glaucoma were excluded. The following data were collected: gender, ethnicity, cause and type of cataract, age at cataract surgery, preoperative measurements (AL, anterior chamber depth, lens thickness, keratometry) and technique of measurement, IOL type and location, presence of glaucoma or ocular hypertension after cataract surgery, and follow-up data including age at follow-up, measurements (AL, anterior chamber depth, keratometry) and technique of measurement, and best corrected visual acuity at final follow-up. Study data were collected and managed using REDCap electronic data capture tools hosted at the Medical University of South Carolina.[3]

All analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA). Descriptive statistics were calculated for demographic information as well as baseline and final visit variables. We considered race initially as a categorical variable with 3 levels (white, African American, or Other). However, because of the limited number of patients in the "Other" racial category, it was decided to collapse race into 2 categories, whites and Other, for all subsequent analysis.

Univariate associations between AL over time with all covariates were examined using a series of generalized estimating equation (GEE) models. The GEE approach is an extension of linear regression within a longitudinal framework where repeated measures are made within every individual; it is also useful in ophthalmic studies where measurements in the 2 eyes of the same person are strongly correlated.[4] This approach allowed us to estimate a population mean for AL over time while accounting for correlation from repeated measures taken on the same individual. We used the univariate models of AL to develop a multivariable model for predicting postoperative AL. All variables with a univariate P value $<.20$ were considered in the multivariable GEE regression models, and backwards selection was used to determine the final model. We also considered both linear and natural log-transformed patient age, as AL growth has been shown in young children to follow a logarithmic relationship with age. All variables with a multivariate significance of $P <.05$ were retained in the final multivariable model. All model assumptions were checked graphically, and variable transformations were considered when needed. Additionally, a marginal R^2 value was calculated for the multivariable models. As an internal validation of model prediction, we employed a resampling approach in which GEE models including baseline globe AL, age at time of surgery, age and follow-up, and the interaction between

TABLE 1. Patient Characteristics by Eye

Variable	Right Eye (n = 64)	Left Eye (n = 64)
Gender, male	34 (53)	—
Race		
White	36 (56)	—
African American	23 (36)	—
Other	5 (8)	—
Age at surgery, yr	6.5 (3.9)	6.4 (3.9)
Final age, yr	13.0 (5.1)	—
Family history of childhood cataract		
Yes	24 (38)	—
No	31 (48)	—
Unknown	9 (14)	—
Type of cataract		
Cortical	13 (20)	15 (23)
Lamellar	23 (36)	21 (33)
Nuclear	8 (13)	8 (13)
Other	20 (31)	20 (31)
Preoperative AL under anesthesia, yes	60 (94)	
Preoperative AL, mm	22.4 (1.6)	22.3 (1.5)
Preoperative ACD, mm	3.7 (0.4)	3.6 (0.4)
Preoperative LT, mm	3.4 (0.6)	3.5 (0.6)
Preoperative keratometry average, D	44.4 (1.9)	44.4 (1.9)
IOL location		
Bag	61 (95)	22 (97)
Piggyback	1 (2)	1 (1.5)
Sulcus	2 (3)	1 (1.5)
IOL type		
AcrySof MA30	3 (5)	0 (0.00)
AcrySof MA60	5 (8)	8 (13)
AcrySof SA60AT	11 (17)	12 (19)
AcrySof SN60WF	33 (52)	33 (52)
Other	12 (19)	11 (17)
Borderline high IOP in pseudophakic eye, yes	3 (5)	3 (5)
Final visual acuity, LogMar	0.18 (0, 1.01)	0.18 (0, 0.70)
Final AL, mm	23.4 (1.6)	23.2 (1.6)
Average follow-up, yr	6.63 (4.0)	6.65 (4.0)

All continuous variables unless otherwise noted are reported as mean (SD) and all categorical variables are reported as n (%).

Characteristics that are the same across both eyes are only reported in the column for the right eye.

ACD = anterior chamber depth; AL = axial length; IOL = intraocular lens; IOP = intraocular pressure; LT = lens thickness.

TABLE 2. Estimated Mean Difference in Axial Length Based on Univariate GEE Models for All Variables

Variable	Difference in AL (95% CI)	*P*
Baseline axial length, 1-mm increase	0.879 (0.770, 0.987)	<.001
Age at baseline, 1-yr increase	0.042 (–0.075, 0.159)	.482
Gender, male vs female	0.803 (0.066, 1.540)	.033
Race, other vs white	0.847 (0.063, 1.632)	.034
Age at follow-up, 1-yr increase	0.125 (0.104, 0.146)	<.001
Time of follow-up, 1-year increase	0.111 (0.082, 0.140)	<.001
Anterior chamber depth, 1-unit increase	0.374 (0.222, 0.526)	<.001
Final visual acuity	1.302 (0.256, 2.347)	.015
Eye, left vs right	–0.166 (–0.295, –0.037)	.012
Type of cataract		
Cortical vs other	0.437 (–0.183, 1.057)	.167
Lamellar vs other	0.135 (–0.440, 0.709)	.645
Nuclear vs other	–1.057 (–2.018, –0.097)	.031
Baseline lens thickness, 1-mm increase	–0.127 (–0.383, 0.129)	.332
Borderline high IOP in pseudophakic eye, yes vs no	0.686 (–0.708, 2.080)	.335
Keratometry average, 1-D increase	–0.039 (–0.112, 0.033)	.290

Values represent the mean change in axial length anticipated for each factor with 95% CI and *P* value.
AL = axial length; D = diopter; GEE = generalized estimating equation; IOP = intraocular pressure.

baseline age and age at follow-up were fit to 10 000 unique subsets of 51 of the 64 subjects selected based on patient ID. Prediction error for each model was then estimated using the 13 subjects excluded when building the model, and mean model prediction error was estimated as the mean difference between the predicted and observed values of AL at last follow-up visit across all 10 000 subsets of data.

RESULTS

SIXTY-FOUR CHILDREN WHO UNDERWENT BILATERAL cataract surgery with primary IOL implantation were identified. The median age at the time of surgery was 5.1 years, with a range from 2.0-17.5 years. All baseline measurements of AL were done with ultrasound biometry using the immersion technique. For 60 (94%) patients, preoperative measurements were obtained under anesthesia before surgery on the first eye. Follow-up measurements were obtained for 178 visits. Median number of visits were 2 (range 1-7). The median age at the final follow-up visit was 12.5 years, with a range from 4.0-28.8 years. Median AL before surgery was 22.2 mm (18.4-26.9), and median AL at the final visit was 23.1 mm (19.57-28.6). Median follow-up time was 5.8 years (1.3-17.6). Nine patients had final AL measurements at age >18 years, 21 patients had final AL at age >15 years, 45 patients had final AL at age >10 years. Best-corrected final visual acuity was recorded for 114 eyes of 57 patients. Median final visual acuity was 20/30. Three participants were reported to have borderline high IOP.

TABLE 3. Multivariable GEE for Axial Length Over Time

Variable	Beta (SE)	*P*
Intercept	1.933 (0.994)	.052
Preoperative axial length, mm	0.914 (0.048)	<.001
Age at baseline, yr	–0.065 (0.055)	.234
Age at follow-up, yr	0.140 (0.018)	<.001
Baseline age × Age at follow-up, yr	–0.005 (0.002)	.029

GEE = generalized estimating equation.

Characteristics of the study population by eye (right/left) are presented in Table 1.

Results for the univariate GEE models of AL are shown in Table 2. Variables significantly associated with AL included age at cataract surgery, gender, race, preoperative AL, preoperative anterior chamber depth, final visual acuity, time of follow-up, and patient age at follow-up. Males have an estimated mean AL 0.80 mm longer than females (*P*=.033), whereas whites have an estimated mean AL 0.84 mm shorter than other races (*P*=.034). AL was similar between African Americans and "Other," but whites had significantly shorter AL relative to African Americans (*P*=.01). AL was not associated with which eye was being measured, type of cataract, baseline lens status, baseline average keratometry or average keratometry over time, or whether or not the patient had borderline high IOP in the pseudophakic eye.

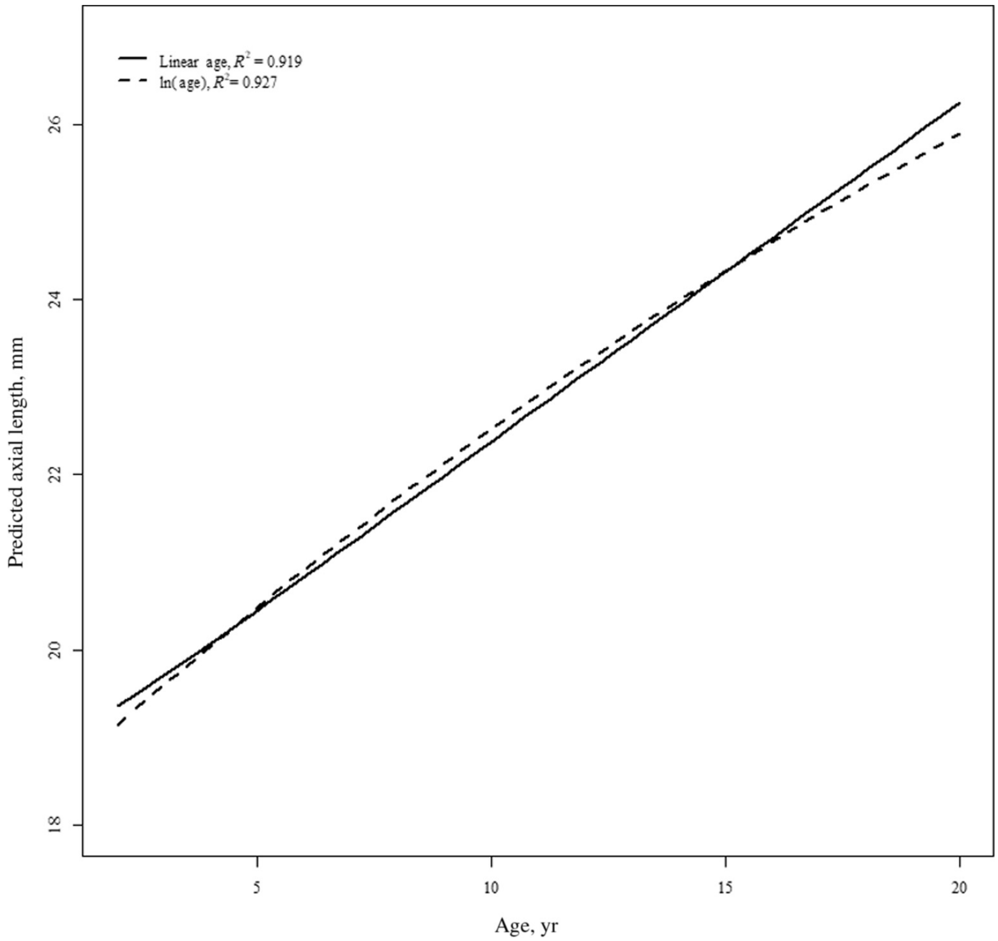

FIGURE 1. Predicted axial length by patient age under linear and natural log-transformed age.

Variables considered in the multivariable GEE model of AL included age at cataract surgery, race, gender, preoperative AL, preoperative anterior chamber depth, and age at follow-up. We also considered the association between AL and the interactions between patient age at baseline and duration of follow-up, patient age at baseline and patient age at follow-up, and patient age at follow-up and duration of follow-up. All 3 interactions were statistically significant; however, given that the goal of the study is to develop a model to predict AL at follow-up, only the interaction between baseline patient age and age at follow-up was considered in the multivariable model. Final visual acuity was also not considered in the model, as it would not be useful in predicting axial growth for patients undergoing surgery. The final model included AL at time of surgery, patient baseline age, age at follow-up, and the interaction between baseline age and age at follow-up. The final model is presented in Table 3, and a linear equation of the model can be written as follows:

Postoperative AL = 1.93 + 0.91 × (baseline AL) – 0.07 × (baseline age) + 0.14 × (age at follow-up) – 0.005 × (baseline age) × (age at follow-up)

The internal validation conducted using resampling found a mean prediction error of –0.052 for AL with an estimated 95% confidence interval of –0.39 to 0.32. The 95% confidence interval for prediction error was estimated by taking the 2.5 and 97.5 percentile values across all 10 000 estimated prediction error rates.

Among the follow-up measurements, for 150 visits, measurements were done using immersion, whereas 28 measurements were done with optical biometry using IOLMaster. A sensitivity analysis was run, which revealed no significant difference when we excluded measurements taken with IOLMaster.

We also fit the above model using the natural log-transformed baseline age and age at follow-up. The model presented above and the model with the log-transformed age variables had marginal R^2 values of 0.92 and 0.93, respectively. Figure 1 presents the predicted AL by patient age under both models.

DISCUSSION

THE PRIMARY PURPOSE OF THIS STUDY WAS TO DEVELOP A model to predict future AL in children undergoing bilateral cataract surgery with primary IOL implantation. Although gender and ethnicity were significantly associated with AL in the univariate models, they were not significant in the final model. We believe this to be the case because, by including baseline AL and age in the final model, we have already accounted for the differences in gender and ethnicity. Keratometry was also not a significant predictor of AL in this patient population. Previous studies have found AL to have a linear relationship with keratometry during infancy, with K values flattening as AL increases.[5] However, K values reach the adult range much earlier than AL values, reportedly stabilizing around 6 months of age.[6] As we were focused on a population over the age of 24 months, K values did not significantly change with time and therefore were not significant predictors of postoperative AL.

The majority of AL measurements were done using A-scan immersion ultrasound; however, a few postoperative measurements were also done using IOLMaster. Studies in adult eyes have found that results obtained by IOLMaster are interchangeable with those obtained by an experienced ultrasonography technician.[7] Lenhart and colleagues compared measurements obtained by IOLMaster with measurements obtained using immersion ultrasonography in 18 children. On average, the IOLMaster-measured ALs were 0.1 mm less than the immersion ultrasonography values.[8] A sensitivity analysis was run, which revealed no significant difference when we excluded measurements taken with IOLMaster, suggesting that measurements of both techniques are similar and can be included in the final model. A future study is still needed, however, to assess the true interchangeability of these two techniques in pediatric eyes.

Currently, most pediatric ophthalmologists use an IOL power calculation preoperatively with measured biometry readings and then adjust the power based on the age of the patient to account for a predicted myopic shift.[9,10] The major challenge with this method is the great deal of uncertainty in refractive change with time; not all 4-year-olds will require +3 diopters of postoperative refraction, for example. An alternative method of IOL power selection would be to predict the child's final AL and then use that AL to calculate IOL power and then undercorrect as needed, rather than adjusting for the estimated change in refraction after the calculation is made.

By knowing a patient's baseline AL and baseline age, we can use the multivariable model to predict AL at a chosen follow-up age with the following equation:

Postoperative AL $= 1.93 + 0.91 \times$ (baseline AL) $- 0.07 \times$ (baseline age) $+ 0.14 \times$ (age at follow-up) $- 0.005 \times$ (baseline age) $\times$ (age at follow-up)

Let us take 2 examples that we mentioned above, for 2 children undergoing cataract surgery at age 3 years with different AL. Calculations below are done using Holladay 1 formula for AcrySof SN60WF IOL.

1. Age at surgery 3 years, preoperative AL 21.95 mm, undercorrection aim 3 D would require a 21-D IOL. Predicted AL at age 20 would be as follows:

Postoperative AL $= 1.93 + 0.91 \times (21.95) - 0.07 \times (3) + 0.14 \times (20) - 0.005 \times (3) \times (20) = 24.19$ mm

If we would have used this predicted AL value in an IOL calculation formula, instead of 21 D, the child would have required 18 D (aiming for emmetropia at age 20). If this child would have been implanted with 18 D instead of 21 D at the time of cataract surgery at 3 years of age, the undercorrection at the time of surgery would be 4.86 D (instead of 3 D). On the other side, with a 21-D implanted IOL at 3 years of age, the child is expected to have a –2.14 D refraction at age 20 instead of emmetropia as estimated at the time of cataract surgery.

2. Age at surgery same as above (3 years), preoperative AL 20.34 mm, undercorrection aim same as above (3 D) would require 30-D IOL. Predicted AL at age 20 would be as follows:

Postoperative AL $= 1.93 + 0.91 \times (20.34) - 0.07 \times (3) + 0.14 \times (20) - 0.005 \times (3) \times (20) = 22.73$ mm

If we would have used this predicted AL value in an IOL calculation formula, the child would have required 25 D instead of 30 D (aiming emmetropia at age 20). If this child would have been implanted with 25 D instead of 30 D at the time of cataract surgery at 3 years of age, the undercorrection at the time of surgery would be 6.27 D instead of 3 D. On the other hand, with a 30-D implanted IOL, the child is expected to have a –3.66 D refraction at age 20 instead of emmetropia as estimated at the time of cataract surgery.

As seen in the above two examples, the undercorrection aim for the child with AL 21.95 mm at the age of 3 years of age would be 4.86 D, whereas at the same age with AL 20.34 mm, the undercorrection aim would be 6.27 D to minimize late myopia. Note that we do not recommend aiming for 3 D at 3 years of age. This is a multifactorial decision based not only on age at surgery and preoperative AL, but also on visual acuity, amblyopia status, and several other factors. In an individual case, it may be better to have a lower undercorrection at the time of surgery even at the cost of higher myopia at age 20, especially if the child has dense amblyopia and compliance with optical and amblyopia therapy is assumed to be poor.

Our axial growth model could potentially be used to make more accurate and customized IOL calculations. Our model takes into account baseline AL and age at surgery, whereas the standard method uses only a table of recommended postoperative refractions based on age at surgery. Figure 2 shows the postoperative change in AL of 3 additional hypothetical patients with different baseline ages and baseline ALs in order to demonstrate how varying baseline measurements result in varying predicted AL values at the same final age. To make pediatric IOL power calculations simpler, we propose the development of an app

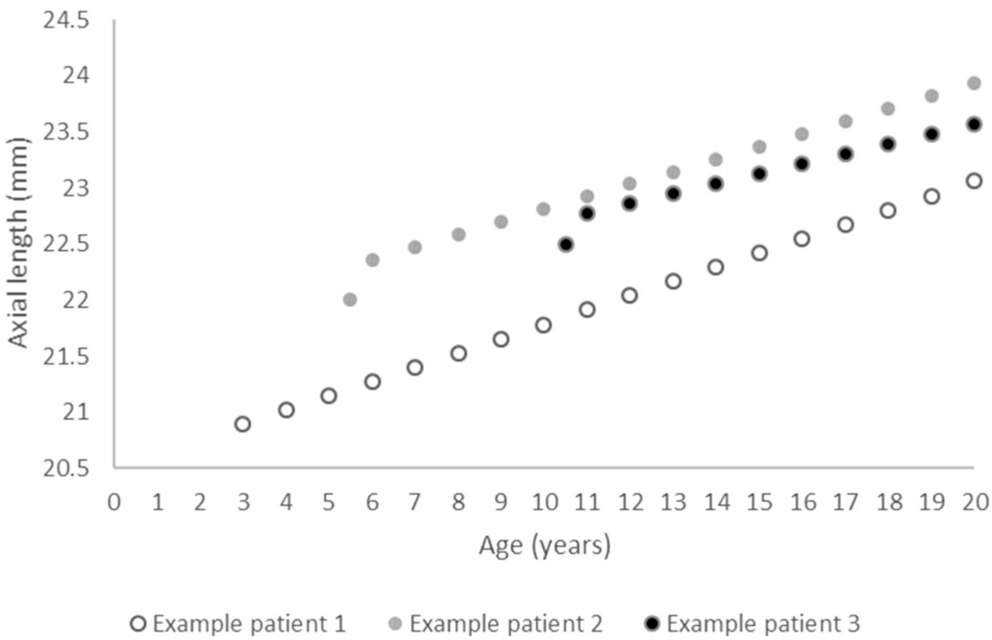

FIGURE 2. Hypothetical examples of change in AL using the final regression model. Example patient 1 has a baseline AL of 20.5 mm at baseline age 2.5 years. Postoperative AL at age 20 years is predicted to be 23.06 mm. Example patient 2 has a baseline AL of 22 mm at baseline age 5.5 years. Postoperative AL at age 20 is predicted to be 23.93 mm. Example patient 3 has a baseline AL of 22.5 at baseline age 10.5 years. Postoperative AL at age 20 years is predicted to be 23.57 mm.

where practitioners can enter baseline measurements and age to generate the estimated final AL of the patient.

Although previous studies have found that logarithmic transformation of age better explains variation in AL, it is true particularly when data from children younger than 18 months are included. As shown in Figure 1 of our previously published biometry data, AL becomes linear or nearly linear in older children.[2] As expected, log transformation did not better fit model assumptions in our data set as we have included only children older than 2 years.

This study was limited by the retrospective nature of the data used. Follow-up time for patients and time between visits were variable. Additionally, not all patients have been followed into adulthood (9 patients had final AL measurements at greater than 18 years of age, 21 patients had final AL at greater than 15 years of age, 45 patients had final AL at age >10 years). Some patients had serial AL measurements over many years, whereas others had 1 postoperative AL measured. An ideal study would observe all patients with regular serial AL measurements from the preoperative visit until adulthood. Additionally, we know that genetics likely plays a role in axial growth and development of myopia; however, we did not have information on the refractive error of the parents. In a future study, it would be useful to ask about the refractive error of the child's parents to know if that makes a difference in predicting AL.

The internal validation we conducted of the proposed prediction model suggests that the model has reasonable prediction error in this study population and only slightly underestimates AL. However, given that the model was developed on 64 unique subjects and not all subjects reached maturity by the end of the study, we would also like to caution readers that this model needs to be externally validated as a prediction model.

The major strength of this study is the amount of data we have collected on AL over time. Also, most AL measurements were done using immersion A-scan. As accurate selection of IOL power for children depends on both the preoperative measurement of AL and a comprehensive understanding of eye growth patterns, monitoring axial elongation over time in children with cataracts is hugely important, and we encourage all pediatric ophthalmologists to document AL measurements of their postoperative patients. Parents often have high expectations that normal vision will be restored, especially if their child develops cataracts later in childhood. This was the first study that we know of to attempt to model postoperative AL in order to improve IOL power calculations. Although there is a theoretical advantage to using this new method, we plan to prospectively test the model in a future study by comparing predicted AL measurements to actual AL measurements in patients following cataract surgery.

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