

# Accuracy of the Majority Voting Method with Multiple IOL Power Formulae

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**Purpose:** This study aimed to evaluate the efficacy of a majority decision algorithm that integrates intraoperative aberrometry (IA) and two intraocular lens (IOL) frequency formulas. The primary objective was to compare the accuracy of three formulas (IA; Sanders, Retzlaff, and Kraff/Theoretical (SRK/T); and Barrett Universal II (BUII)), in achieving emmetropia in eyes implanted with TFNT lenses (Alcon).

**Patients and Methods:** A total of 145 eyes of 145 patients were included in the evaluation. Preoperative data were obtained from IOLMaster 700, while intraoperative data were collected from ORA SYSTEMTM. Visual acuity  $\geq 0.8$  at the 3-month post-surgery mark was confirmed. We assessed refractive prediction error (RPE), which is the difference between predicted refraction (PR) and postoperative subjective refraction. This evaluation aimed to identify the optimal IOL power with the implemented algorithm.

**Results:** Among the 145 eyes evaluated, 55.9%, 78.7%, and 97.2% achieved postoperative subjective refraction within  $\pm 0.13$  Diopters (D),  $\pm 0.25$  D, and  $\pm 0.50$  D, respectively. The percentages of eyes within  $\pm 0.25$  D of PR varied by formula type, with values of 57%, 57%, and 54% for IA, BUII, and SRK/T, respectively. For eyes with short to medium axial length (AL < 26.00 mm), the percentages within  $\pm 0.25$  D of RPE were 52%, 58%, and 58% for IA, SRK/T, and BUII, respectively. In contrast, for eyes with long axial length ( $\geq 26.00$  mm) the percentages were 68%, 52%, and 45% for IA, BUII, and SRK/T, respectively.

**Conclusion:** The proposed majority decision algorithm incorporating IA and two IOL frequency formulas was effective in reducing postoperative refractive error. IA was particularly beneficial for eyes with long axial length. These findings suggest the algorithm has potential to optimize IOL power selection to improve quality of life of patients and clinical practice outcomes.

**Keywords:** multifocal intraocular lens, cataract, intraocular lens power calculation, axial length, optimum visual acuity

## Introduction

In cataract surgery, the appropriate choice of intraocular lens (IOL) power has a significant impact on patient quality of life. IOL power is selected based on ocular biometric data and calculations used to determine the predicted refraction (PR). A difference between PR and actual postoperative refraction is refractive prediction error (RPE). In particular, multifocal IOL implants require higher PR accuracy than monofocal IOL implants. In recent years, IOL power calculation formulas that use multiple ocular parameters and/or incorporate artificial intelligence to derive PR have been used.

The third-generation Sanders, Retzlaff, and Kraff/Theoretical (SRK/T) formula is calculated using only two parameters, which are axial length (AL) and corneal radius. It had a limitation in that RPE was greater in eyes with AL that differed significantly from average.<sup>1</sup> To address this, the fifth generation Barrett Universal II (BUII) formula incorporated the additional parameters of anterior chamber depth, lens thickness, and corneal diameter.<sup>2-6</sup> Furthermore, Hill-RBF and

Kane formulas, which incorporate artificial intelligence, have recently emerged and been reported to have comparable or better PR accuracy than BUII.<sup>7–9</sup>

Intraoperative measurements, by wavefront aberrometer ORA SYSTEM™ (Alcon Laboratories, Inc.), of spherical power and astigmatism were used to calculate IOL power based on PR. Intraoperative aberrometry (IA) has been associated with good postoperative outcomes in eyes following corneal refractive surgery.<sup>10–12</sup> A study comparing PR by IA with those by Haigis-L and Shammas formulas in myopic laser in situ keratomileusis (LASIK) cases reported PR by IA showed the lowest RPE, with a median absolute error of 0.35 D.<sup>10</sup> In eyes with prior radial keratotomy, RPE for IA was 0.48 D and that for Barrett True K No History was 0.50 D with no significant difference between them and both considered good.<sup>12</sup> However, among IA, BUII, and Hill-RBF used for eyes with no history of corneal refractive surgery, it was reported that IA did not improve RPE.<sup>13,14</sup>

Barrett is reported to have good results,<sup>15</sup> but the formula alone has limitations and often does not match intraoperative ORA data. In the present study, we assessed a majority decision algorithm, which includes IA, SRK/T, and BUII, to determine IOL power in patients with no history of corneal refractive surgery. The algorithm has the following six steps.

Preoperative examination to measure AL, corneal radius, corneal diameter, anterior chamber depth, and lens thickness. Calculation of IOL power by SRK/T and by BUII to obtain two PR values. Intraoperative examination by IA to measure spherical and astigmatism powers to obtain a third PR value. Examination of the three PR values to determine the final PR by majority decision. Selection of an IOL power closest to that which is predicted to provide negative postoperative refraction to avoid a decline in near visual acuity (VA). And, in this study, evaluation of RPE by calculating the difference between each PR and 3-month postoperative refractive error. To assess the algorithm, we examined and compared the effects of each component.

## Material and Methods

Patients that underwent cataract surgery and AcrySof® IQ PanOptix® Trifocal Lens (Model: TFNT, Alcon Laboratories, Inc., Fort Worth, Texas, USA) implantation at Chukyo Eye Clinic from June 2019 to April 2021 aiming for emmetropia were followed-up. The study investigated 244 eyes in 145 patients with an IOL permanently fixed within the capsule achieving  $\geq 0.8$  corrected VA by decimal VA chart at 3-month follow-up. VA criteria were established to evaluate stable power without power fluctuation due to ocular diseases such as dry eye. We used measurements taken at the 3-month follow-up because results of a Japanese clinical trial showed that power was considered stable by this time.<sup>16</sup> Of those who had surgery in both eyes, the first eye to be operated was selected and 145 eyes were enrolled. The mean $\pm$ SD age was 62.1 $\pm$ 12.1 yrs. (male: female = 57:88); AL, 24.98 $\pm$ 1.84 mm (range 21.94–30.35); corneal refractive power, 43.97 $\pm$ 1.37 D (range 40.83–48.15); and corneal astigmatism, 0.95 $\pm$ 0.64 D (range 0.12–3.74). The TFNT types were TFNT00 (95 eyes), TFNT30 (28 eyes), TFNT40 (10 eyes), TFNT50 (9 eyes), and TFNT60 (3 eyes). Toric style was determined using the Alcon web calculator. Astigmatism was determined using the corneal total refractive power (Real cylinder) of the anterior segment OCT CASIA2 (Tomey, Aichi, Japan). The use of Toric was considered for astigmatism of 1.0 D or higher.

The required sample size was calculated using EZR (Easy R, version 1.41) for medical statistics.<sup>17</sup> EZR is available at (<http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>) and runs on both Windows (Microsoft Corporation, USA) and Mac OS X (Apple, USA). In a prior experiment with 10 patients, the mean difference in refractive error in IA and BUII was 0.03 and the standard deviation common to the two groups was 0.33, so the sample size was calculated to be 136 when the non-inferiority margin was set at 0.1, the significance level at 5% and power at 90%.

The study was approved by Chukyo Eye Clinic Ethics Committee (No. 20,210,823–01) and adhered to the tenets of the Declaration of Helsinki. Due to its retrospective design, the Ethics Commission approved an opt-out method for inclusion of patient data which maintains anonymity instead of requiring written informed consent.

## Measurement of intraoperative aberrometry and two IOL frequency formulas

IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany) was used to obtain preoperative measurements of parameters used in IOL power calculations by SRK/T and BUII formulas to find two respective PR values. Further measurements by IA were taken intraoperatively, a third PR value was obtained and IOL power was determined. The majority rule we employed evolved over years of clinical experience evaluating and comparing methods for calculating IOL power to

reduce RPE. Briefly, since 2016 we had been conducting preliminary experiments using ORA to accumulate clinical data, with the same results as previously reported for RPE.<sup>18,19</sup>

The selection method was based on the IOL power closest to 0D in absolute value of the predicted refraction value by BU II. Additionally, the predicted values of IA and SRK/T were cross-referenced with the IOL frequencies determined in BU II. The IOL power was chosen to ensure that two or more of the three equations' predicted refraction values had a negative sign.

For the A constant, we used a value optimized by our clinic having refined it based on our clinical experience and past outcomes. Thus, the A constant was set at 119.3 and a Lens factor (LF) of 2.04 was used. The surgeon factor of the intraoperative aberrometer was optimized four times during the period using our data. A flowchart of the process is depicted in Figure 1. Patients with a history of ocular surgery, including refractive surgery, and intraoperative complications were excluded.

Outcome measures were as follows: 1) Subjective refraction (spherical equivalent power, SE) of patients reported at 3-month follow-up were examined. 2) Comparison of SE with IA, SRK/T and BU II at RPE. 3) RPE for IA, SRK/T, and BU II were examined. 4) Cases with a RPE of BU II  $>\pm 0.25$  D were examined for any difference in parameters between eyes with small IA RPE and large IA RPE. 5) RPE by AL.

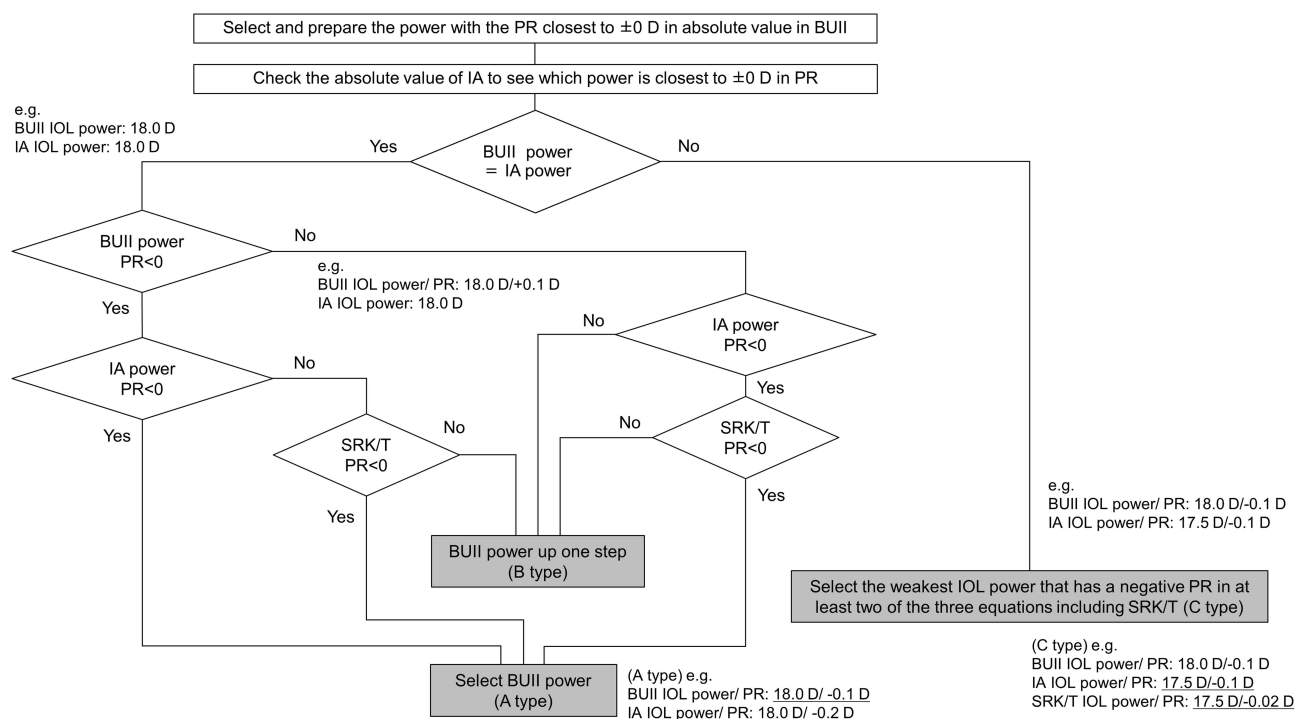
## Statistical Analysis

Data were statistically analyzed as follows: Shapiro–Wilk test for normality. One-way repeated measures ANOVA or Friedman Test to compare RPE. Cochran's Q Test to compare percentages of RPE. Student's *t*-test to compare items within and between groups. The required sample size was calculated with power calculation software EZR.

## Results

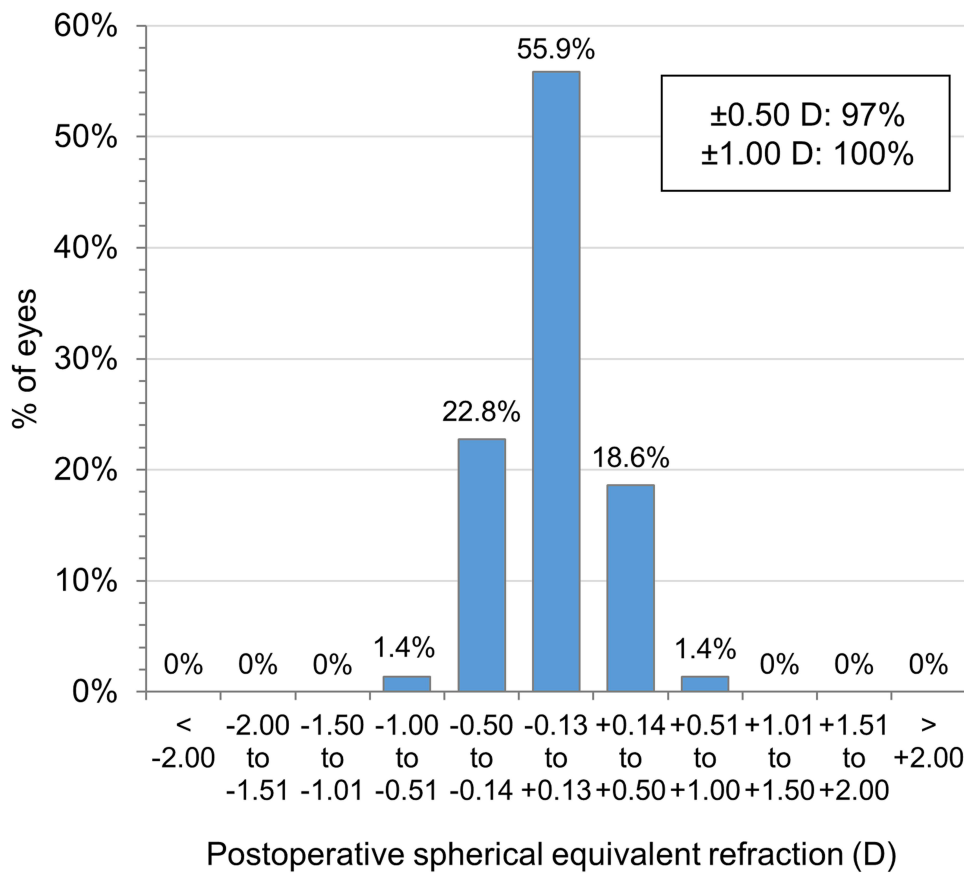
### SE at 3-month post-surgery and difference between SE and RPE by formula

Of the 145 eyes, 81 (55.9%) had SE within  $\pm 0.13$  D, 115 (78.7%) within  $\pm 0.25$  D, and 141 (97.2%) within  $\pm 0.50$  D (Figure 2). Among the three formulas, the number of cases with the smallest refractive error was 55 eyes for IA, 44 for SRK/T and 46 for



**Figure 1** Flowchart of majority decision algorithm using BU II, IA, and SRK/T. In BU II and IA, IOL frequencies with the absolute-value of PR closest to  $\pm 0$  D were defined as BU II power and IA power.

**Abbreviations:** PR, Predicted Refraction value; BU II, Barrett U II; IA, Intraoperative Aberrometry.



**Figure 2** Eyes (%) by SE at 3-month post-surgery and relationship between RPE and SE in each formula of the 145 eyes, 115 (78.7%) were within  $\pm 0.25$  D and 141 (97.2%) within  $\pm 0.50$  D.

BU II. When examining the results from individual formulas, no formula demonstrated superiority. Specifically, 45 cases consistently showed results within  $SE \pm 0.25$  D for all IA, SRK/T and BUI. Additionally, 38 cases fell within  $SE \pm 0.25$ D for two calculation methods, while 18 cases for IA, 13 for SRK/T and 5 for BUIII showed this threshold within a single calculation method. The total number of cases for each formula was 84 eyes for IA, 81 for SRK/T and 82 for BUIII (Table 1). The number of cases where both SE and RPE were minimized for each calculation formula were 53 cases for IA, 42 for SRK/T, and 44 for BUIII. Furthermore, there were two cases where SE and RPE were minimized for both IA and SRK/T, one case for SRK/T and BUIII, two cases for IA and BUIII, and only one case where SE and RPE were equally minimized for all calculation formulas (Table 2).

No eyes had  $SE \geq \pm 1.01$  D. Based on the flowchart in Figure 1, eyes were classified into A–C types. Sixty-three eyes (43.4%) were type A and the IOL power planned for BU II was inserted. Of these, 98.4% had SE within  $\pm 0.5$  D. Sixteen

**Table 1** Distribution of cases with RPE within  $SE \pm 0.25$ D (119 eyes)

	IA (n=83)	SRK/T (n=79)	BUIII (n=82)
ALL	43		
IA and SRK/T	6		
SRK/T and BUIII		17	
IA and BUIII	16		(16)
Alone	18	13	6

**Table 2** Cases with both SE and RPE minimized (145 eyes)

	IA (n=58)	SRK/T (n=46)	BUII (n=48)
Alone	53	42	44
IA and SRK/T	2		
SRK/T and BUII		1	
IA and BUII	2		(2)
ALL	1		

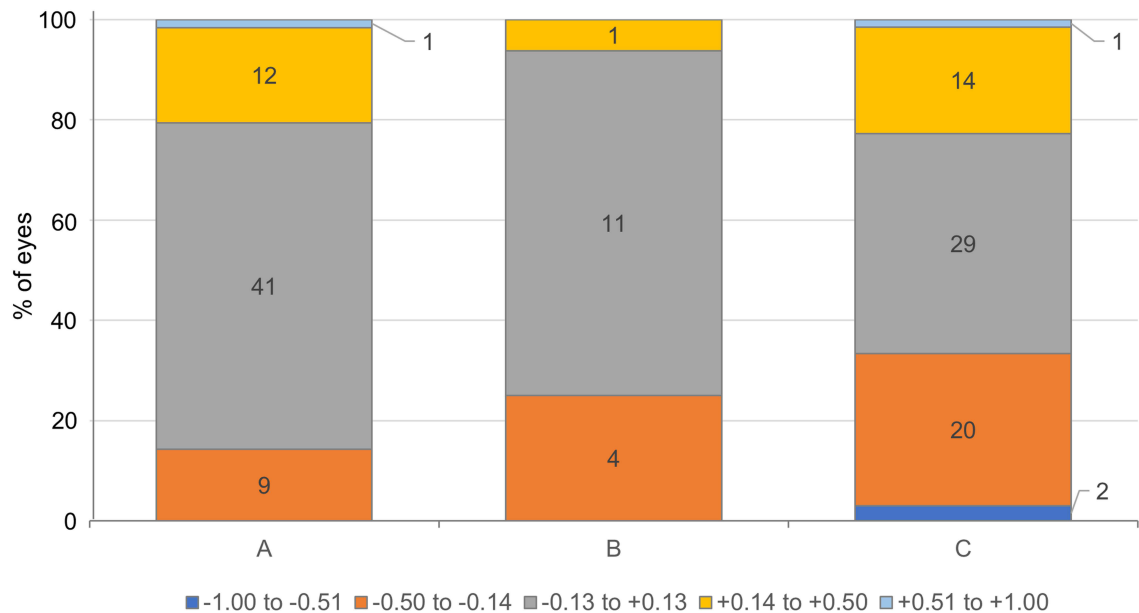
eyes were type B, and an IOL was inserted 0.5 D higher than the planned IOL power in BU II. The B type cases had a previous SE within  $\pm 0.5$  D. Sixty-six eyes were C type, and the IOL power was selected so that the PR had a negative sign in two or more equations based on the predicted postoperative values of the three equations. Of these, the proportion of SEs within  $\pm 0.5$  D was 95.5% (Figure 3).

### RPE for IA, SRK/T, and BUII

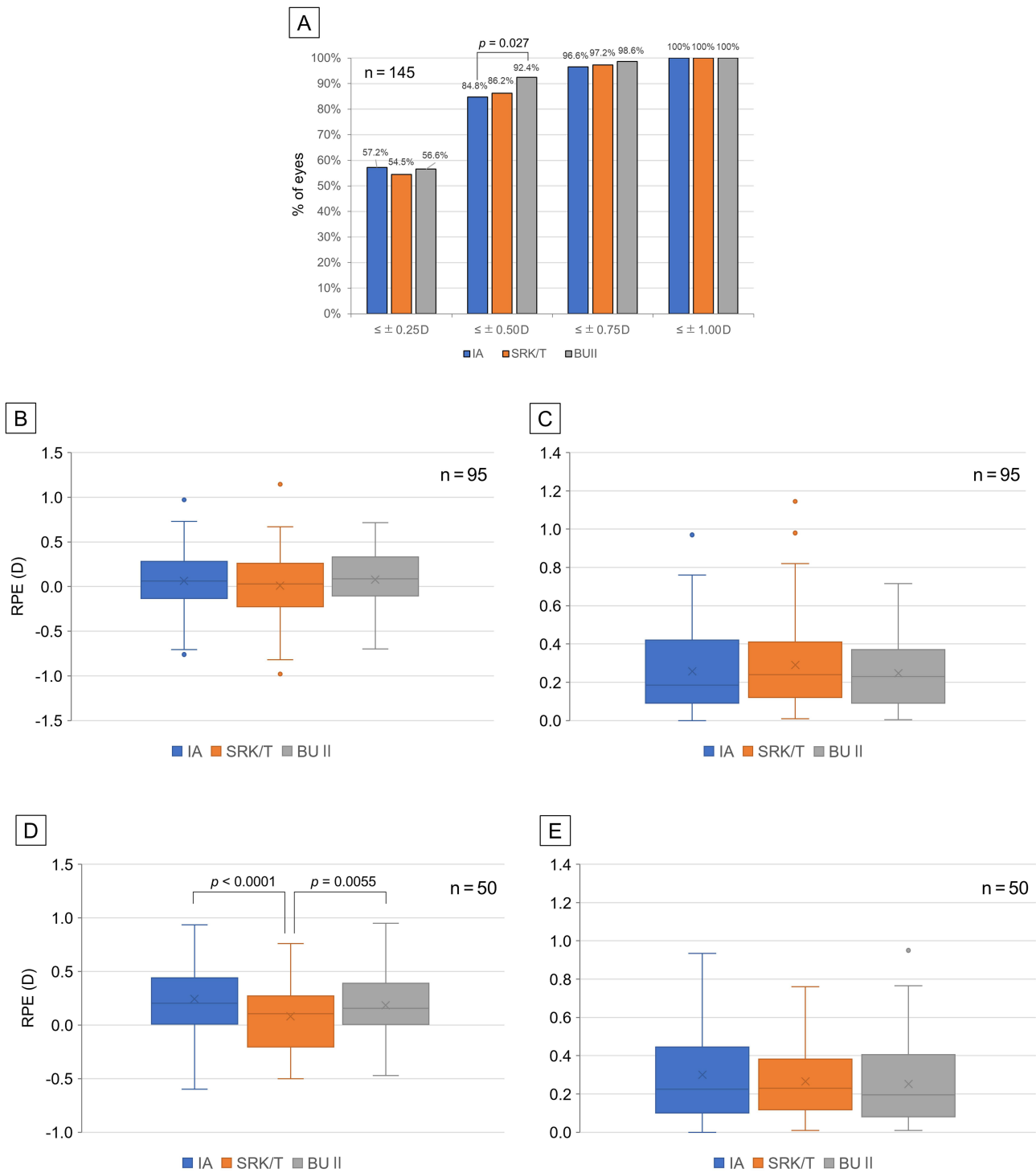
The proportion of eyes with RPE is shown in Figure 4A. The proportion that had RPE within  $\pm 0.25$  D was 83 (57.2%) for IA, 79 (54.5%) for SRK/T, and 82 (56.6%) for BUII; and within  $\pm 0.50$  D was 123 (84.8%) for IA, 125 (86.2%) for SRK/T, and 134 (92.4%) for BUII ( $p = 0.002$ ). Multiple comparison tests showed IA had a significantly lower proportion of eyes with RPE less than  $\pm 0.50$  D than did BUII ( $p = 0.027$ ).

For RPE, non-Toric and Toric cases are presented separately. The arithmetic mean and median RPE values of non-Toric cases did not differ significantly between IA (mean  $\pm$  SD;  $0.06 \pm 0.33$ D, median; 0.06D), SRK/T (mean  $\pm$  SD;  $0.01 \pm 0.37$ D, median; 0.03D) and BU II (mean  $\pm$  SD;  $0.08 \pm 0.29$ D, median 0.09D), as shown in Figure 4B. Similarly, the absolute and

	A (n=63)	B (n=16)	C (n=66)
$\leq \pm 0.50$ D	98.4%	100%	95.5%
$\leq \pm 1.00$ D	100%	100%	100%



**Figure 3** Eyes (%) by percentage of postoperative SE by type. A total of 145 eyes were selected for types A to C.



**Figure 4** Percentage of RPE and arithmetic mean and absolute-value mean by RPE. **(A)** Multiple comparison test results showed significantly lower RPE for IA than for BU II; **(B)** The arithmetic mean of RPE at non-Toric; **(C)** The absolute-value mean of RPE at non-Toric; **(D)** The arithmetic mean of RPE at Toric; **(E)** The absolute-value mean of RPE at Toric.

median RPE values were comparable among IA (mean  $\pm$  SD;  $0.26 \pm 0.21D$ , median;  $0.19D$ ), SRK/T (mean  $\pm$  SD;  $0.29 \pm 0.22D$ , median;  $0.24D$ ), BU II (mean  $\pm$  SD;  $0.25 \pm 0.17D$ , median;  $0.23D$ ), with no significant differences observed (Figure 4C).

**Table 3** Parameters of the good IA and good BUII groups

	IA (n=32)	BUII (n=31)	p value (t-test)
AL	25.51 ± 2.24 mm	24.45 ± 1.83 mm	0.045*
Pre-op. ACD	3.31 ± 0.42 mm	3.38 ± 0.50 mm	0.548
Pre-op. K	44.25 ± 1.67 D	43.88 ± 1.44 D	0.346
Lens thickness	4.46 ± 0.58 mm	4.38 ± 0.60 mm	0.680
Lens thickness /AL	0.18 ± 0.03	0.18 ± 0.03	0.519
White-to-white	11.83 ± 0.38 mm	11.93 ± 0.42 mm	0.334

**Abbreviations:** AL, axial length; ACD, anterior chamber depth; K, keratometry-corneal power; statistically significant\*.

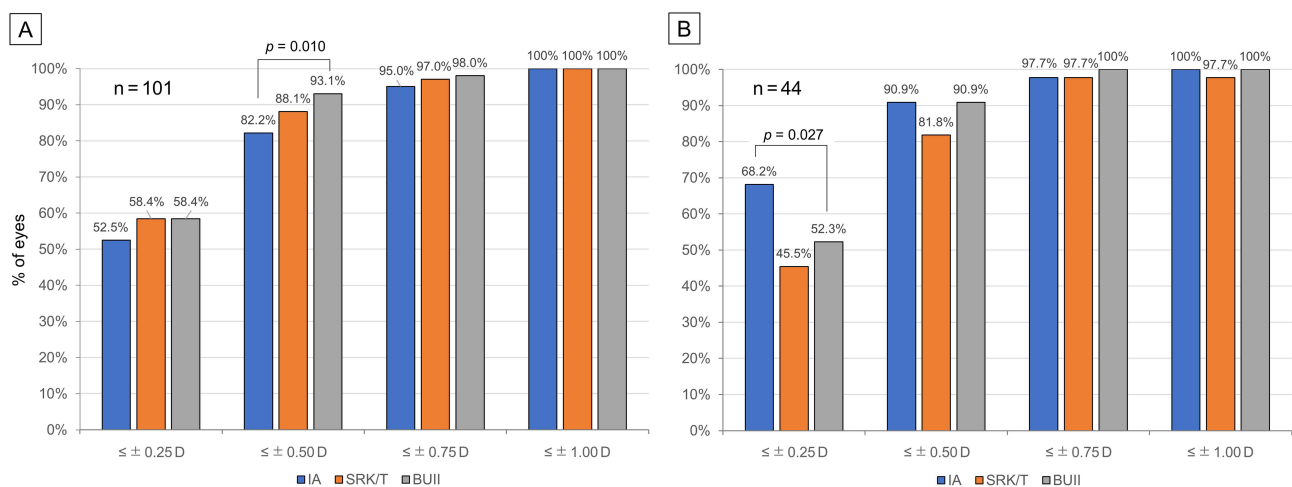
In contrast, the arithmetic mean and median RPE of Toric cases differed significantly between IA (mean ± SD; 0.24 ± 0.32D, median; 0.21D), SRK/T (mean ± SD; 0.08 ± 0.31D, median; 0.11D) and BU II (mean ± SD; 0.18 ± 0.28D, median; 0.16D), with  $p < 0.0001$ . Multiple comparisons revealed that SRK/T had predominantly smaller RPE than IA ( $p < 0.0001$ ) and BUII ( $p = 0.0055$ ) as depicted in Figure 4D. However, the absolute and median RPE values of IA (mean ± SD; 0.30 ± 0.26D, median; 0.23D), SRK/T (mean ± SD; 0.27 ± 0.18D, median; 0.23D), BUII (mean ± SD; 0.25 ± 0.21D, median; 0.20D) did not differ significantly (Figure 4E).

## Parameters associated with RPE of BUII and IA

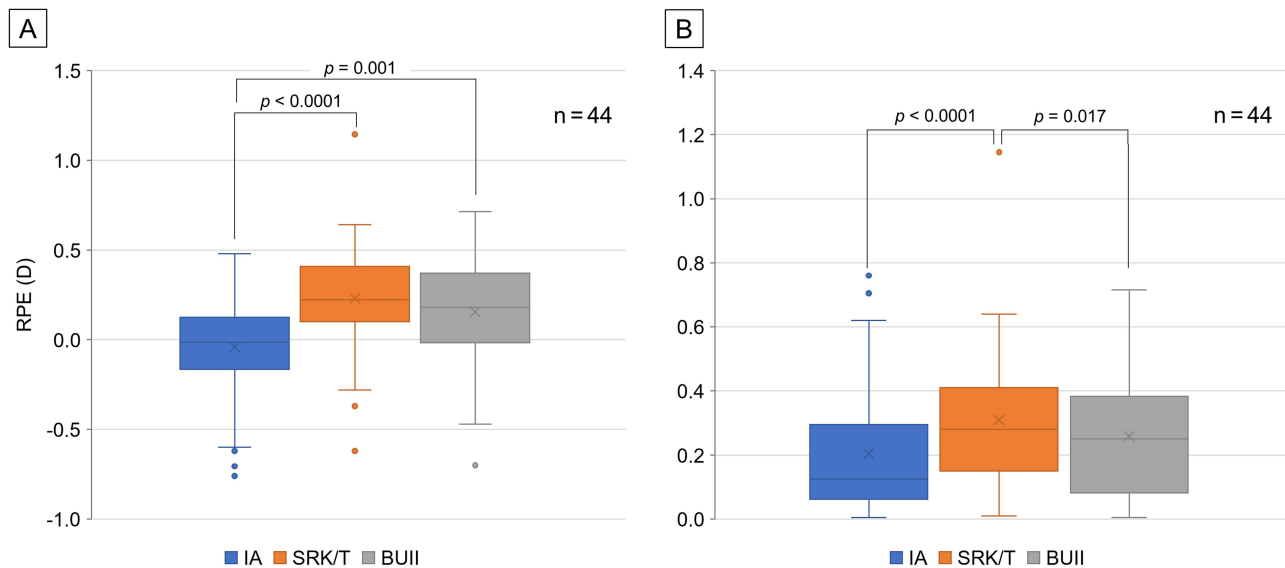
Of the 145 eyes, 63 had RPE  $\geq \pm 0.25$  D when IOL power was calculated using BUII, as shown in Table 3. Among these IA IOL power in 32 showed smaller RPE and was classified as good IA group while 31 eyes in which the RPE by BUII was smaller than that by IA were classified as good BUII group. Comparison of parameters between these two groups found AL was significantly longer in the good IA (25.51 ± 2.24 mm) than good BUII group (24.45 ± 1.83 mm,  $p = 0.045$ ).

## RPE by AL

Eyes were classified into two groups by AL length. In the short ( $n=1$ ) and standard ( $n=100$ ) AL group (AL < 26.00 mm,  $n=101$ ), the proportion of eyes within  $\pm 0.25$  D of PR by calculation method was 52.5% for IA, 58.4% for SRK/T, and 58.4% for BUII ( $p = 0.581$ ); and within  $\pm 0.50$  D of PR was 82.2% for IA, 88.1% for SRK/T, and 93.1% for BUII ( $p = 0.013$ ). Multiple comparison tests showed that IA calculation resulted in significantly lower accuracy than did BUII ( $p = 0.010$ ) (Figure 5A).



**Figure 5** RPE by AL. (A) RPE for short and standard (<26.00 mm) AL group; (B) RPE for long ( $\geq 26.00$  mm) AL group.



**Figure 6** Arithmetic mean and absolute-value mean RPE of the long AL group. **(A)** The arithmetic mean of RPE; **(B)** The absolute-value mean of RPE.

In the long AL group (AL  $\geq$  26.00 mm, n=44), the percentages of eyes within  $\pm 0.25$  D of PR by calculation method were 68.2% for IA, 45.5% for SRK/T, and 52.3% for BUII ( $p = 0.016$ ); within  $\pm 0.50$  D of PR were 90.9% for IA, 81.8% for SRK/T, and 90.9% for BUII ( $p = 0.338$ ). Multiple comparison tests showed that IA calculation resulted in significantly higher accuracy than did SRK/T ( $p = 0.027$ ) (Figure 5B).

In the long AL group, the arithmetic mean, and the median refractive error differed significantly among the three calculation methods: IA (mean  $\pm$  SD;  $-0.04 \pm 0.28$  D, median;  $-0.02$  D), SRK/T ( $0.23 \pm 0.30$  D,  $0.22$  D), and BUII ( $0.16 \pm 0.29$  D,  $0.18$  D) ( $p < 0.0001$ ). Multiple comparison tests showed that IA calculation resulted in significantly lower accuracy than did SRK/T ( $p < 0.0001$ ) and BUII ( $p = 0.001$ ) (Figure 6A). The absolute-value mean, and median refractive errors differed significantly among the three calculation methods: IA (absolute-value mean  $\pm$  SD;  $0.20 \pm 0.20$  D, median;  $0.12$  D), SRK/T ( $0.31 \pm 0.22$  D,  $0.28$  D), and BUII ( $0.26 \pm 0.19$  D,  $0.25$  D) ( $p < 0.0001$ ). Multiple comparison tests showed that IA calculation resulted in significantly lower accuracy than did SRK/T ( $p < 0.0001$ ) and SRK/T calculation resulted in significantly higher accuracy than did BUII ( $p = 0.017$ ) (Figure 6B).

## Discussion

Previously, in a study comparing preoperative IOL power calculations for TFNT implantation aiming for postoperative emmetropia, we reported that the first negative IOL power determined by BUII formula was selected in most cases. The overall percentage of eyes showing SE within  $-0.13$  to  $+0.13$  D at 6-month postoperative was 25%, and that within  $\pm 0.50$  D was 79%.<sup>20</sup> Another study reported that for hyperopic eyes with a maximum AL of 22.5 mm, the percentage of eyes with SE within  $-0.13$  to  $+0.13$  D ranged from 37 to 43%, and that within  $\pm 0.50$  D ranged from 95 to 99%.<sup>21</sup> These findings suggest there is a limitation in achieving postoperative SE within  $-0.13$  to  $+0.13$  D using a single formula available at the time.

In the results of this study, the number of cases where RPE was within  $SE \pm 0.25$  D for all three formulas was 43 (29.65%), indicating that in some cases, different formulas yielded RPE within  $SE \pm 0.25$  D. It has become evident that relying solely on a single formula to ensure RPE within  $SE \pm 0.25$  D is challenging. Therefore, we developed a combination method and applied it in clinical practice. According to the clinical survey by The Japanese Society of Cataract and Refractive Surgery (JSCRS) in 2023, the main formulas used in Japan are SRK/T and BUII.<sup>22</sup> Since SRK/T and Barrett are the two most common formulas used in Japan, they were used in this study. Furthermore, the reason for incorporating IA this time is that, unlike other formulas, IA requires intraoperative data. Since there is only one formula that requires intraoperative data, we devised a method of combining the three formulas in this study. While SRK/T and BUII were adopted in this study, we acknowledge that other formulas could be substituted. Our study is not aimed at



these particular formulas but to point out that a multiple formula approach may render better results than any particular formula. As more formulas are devised, the method employed here may be employed in further comparative studies with larger numbers of cases.

Calculation of IOL power using SRK/T formula requires only two parameters: AL and corneal radius. Recent formulas have introduced additional parameters leading to a reduction in postoperative refractive error. In our report mentioned above, by SRK/T formula the percentage of eyes achieving RPE within  $\pm 0.50$  D was approximately 70%. The percentage of eyes achieving RPE within  $\pm 0.50$  D by BUII formula was reported to be 84%, however, that within  $\pm 0.25$  D was  $< 50\%$ .<sup>13</sup> Even using formulas such as Hill-RBF and Kane that incorporate artificial intelligence, the percentage of eyes achieving RPE within  $\pm 0.25$  D remained below 50%.<sup>23</sup> In the current study, the percentages of eyes achieving RPE within  $\pm 0.25$  D were 57.2% for IA, 56.6% for BUII, and 54.5% for SRK/T. These results compare favorably with those of previous reports, albeit not significantly better.

In the present study, preoperative calculations were performed using SRK/T and BUII formulas to determine the provisional IOL power then intraoperative measurements were obtained by IA to refine and select the final IOL power with a preference for negative postoperative refraction to avoid reduced near VA. While performing IA in all cases may be impractical due to time constraints in surgery, it is important to note that the refractive error of multifocal IOL requires a higher level of accuracy. This method showed a favorable outcome with 55.9% of eyes achieving postoperative SE within the range of  $-0.13$  to  $+0.13$  D and almost all (97.2%) within  $\pm 0.50$  D. It is considered necessary to determine the implanted power based on the predicted values from multiple formulas. BUII was less sensitive to AL and corneal radius and considered to have smaller RPE than SRK/T.<sup>24</sup> Therefore, BUII should be the primary choice to calculate IOL power preoperatively. However, with BUII alone, only 56.6% of eyes showed RPE within  $\pm 0.25$  D. In the 43.4% of eyes that showed RPE  $\geq \pm 0.25$  D with BUII alone we examined the effect of IA and found IA was useful for eyes with long AL. IA achieved significantly better RPE than did SRK/T and BUII in eyes with long AL. In the future, we intend to compare this majority decision algorithm with other ways to utilize the PR values obtained from the three methods such as synthesizing the PR values with a formula that weighs each by its performance history. The ultimate purpose is to harness the strengths of each and minimize the potential limitations or errors associated with any single formula in order to improve the accuracy of PR and reduce RPE. Of course, increasing the accuracy of refractive prediction involves more time. But we expect this time to be a good investment in patient quality of life and clinic reputation.

This study had some limitations. This was a retrospective study. Usefulness of IA was confirmed only in eyes with long AL. Since there was only one eye with short AL in the study population, we were unable to confirm its usefulness in such eyes. Not all eyes were operated on by the same surgeon, so intraoperative differences may exist. All eyes were Japanese, and as only TFNT implants were involved the algorithm needs to be evaluated with other models of IOL. It might be considered by some that including toric and spherical IOL together is a limitation because prediction error or toric calculation may be a confounding variable to some degree, however no adjustments have been made in IA since the toric model was introduced. Moreover, determining spherical power accurately remains crucial for toric IOL, and whether toric were used or not made no difference to the outcomes of this study. A difference that makes no difference is not a significant difference. Recently, it was reported that both IA and the Barrett toric calculator yielded reliable and comparable refractive outcomes for toric IOL implantation.<sup>25</sup>

## Conclusion

The majority decision method of IOL power selection, which combines the BUII and SRK/T formulas with the results of IA, showed good predictive refractive error. IA, in particular, was found to reduce refractive error when used in eyes with long AL.

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pharmaceuticals, outside the submitted work. Dr Kazuo Ichikawa reports research expense from Alcon Japan Ltd, outside the submitted work. The authors report no other conflicts of interest in this work.

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