Meta-analysis of accuracy of intraocular lens power calculation formulas in short eyes

Qiwei Wang MD,1* Wu Jiang MD,2* Tiao Lin PhD,3* Xiaohang Wu MD,1 Haotian Lin MD1§ and Weirong Chen MD1§

1State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, Guangdong, 510060, People’s Republic of China; 2Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou, Guangdong, CN510060, People’s Republic of China;

3 The First Affiliated Hospital, Sun Yat-sen University, ZhongShan Er Road 58#, Guangzhou, Guangdong, CN 510060, People’s Republic of China

*These authors contributed equally to this work.

§Corresponding authors: Haotian Lin, Zhongshan Ophthalmic Center, Xian Lie South Road #54, Guangzhou, China, 510060
Email: haot.lin@hotmail.com
And
Weirong Chen, Zhongshan Ophthalmic Center, Xian Lie South Road #54, Guangzhou, China, 510060
E-mail: chenwr_q@aliyun.com;

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Importance: Intraocular lens (IOL) power selection is a critical factor affecting visual outcome after IOL implantation in short eyes. Many formulas have been developed to achieve a precise prediction of the IOL power. However, controversy regarding the accuracy remains.

Background: To investigate the accuracy of different IOL power calculation formulas in short eyes.

Design: Meta-analysis

Participants: Patients with the axial length of eyes less than 22mm from previously reported studies.

Methods: A comprehensive search in Pubmed, EMBASE, Cochrane Data Base of Systematic Reviews and the Cochrane Central Register of Controlled Trials was conducted by October 2016. We assessed the methodological quality using a modified QUADAS-2 tool and performed analysis on weighted mean differences of mean absolute errors (MAE) among different formulas.

Main outcomes measures: the between-group difference of MAE was evaluated with weighted mean difference and 95% confidence intervals.

Results: Ten observational studies, involving 1161 eyes, were enrolled to compare six formulas: Haigis, Holladay 2, Hoffer Q, Holladay 1, SRK/T and SRK II. Among them, the Holladay 2 introduced the smallest overall MAE (0.496D) without statistical significance. The difference of MAE is statistically significant between Haigis and Hoffer Q (mean difference=-0.07D, p=0.003), Haigis and SRK/T (mean difference=-0.07D, p=0.009), Haigis and SRK II (mean difference=-0.41D, p=0.01). For publication bias and small-study effect, neither funnel plot nor egger’s test detected statistical finding.

Conclusions: The overall evidence from the studies confirmed the superiority of Haigis over Hoffer Q, SRK/T and SRK II in prediction IOL power in short eyes.

Keywords: Short eyes; Cataract; Intraocular lens power; Mean absolute errors

INTRODUCTION

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Improvements in surgical technique, instrument, and intraocular lens (IOL) design enable a better outcome of the cataract surgeries and raise the expectations of the patients at the same time. Comorbidity of patients, the experience of the surgeons, IOL selection, and other factors have an impact on the visual outcome. Among them, the selection of IOL, a quality indicator of cataract surgery\(^1\), accounts for the most cases in cataract surgery claims litigations\(^2\).

For short eyes, commonly defined as AL less than 22mm\(^3\), the IOL power calculation formulas are less accurate than normal\(^3-8\), which presents challenges for cataract surgeons. Since Fyoderov and co-workers\(^9\) first used vergence formulas to estimate the IOL power in 1967, the formulas progress rapidly. The 1\(^{\text{st}}\)-generation formulas use only one constant to estimate the IOL power while the widely used 3rd-generation formulas (SRK/T, Holladay 1 and Hoffer Q) incorporate axial length (AL) and corneal curvature based on thin-lens optical principles. The 4\(^{\text{th}}\)-generation formulas (Holladay 2, Haigis and Olsen) add more parameters to improve the accuracy of estimating the postoperative anterior chamber depth (ACD). For example, Holladay 2 includes AL, keratometry, preoperative ACD, lens thickness, corneal diameter, patient’s age and preoperative refraction\(^10\).

Although some of the early studies considered Holladay 2 as one of the most precise IOL formulas\(^10, 11\), the majority showed no significant difference in accuracy among the formulas (Haigis, Holladay 2, Hoffer Q, Holladay 1, SRK/T and SRK II) for patients with short AL\(^7, 12-15\). Only a few reports detected the significant difference. Maclaren\(^16\) and Moschos\(^17\) suggested Haigis was significantly more precise than Hoffer Q. Day\(^18\) and Gavin\(^19\) reported Hoffer Q produced smaller mean absolute errors (MAE) than SRK/T. Although Olsen showed potential accuracy\(^20\), it is not readily available on the most adopted software and its superiority still needs to be further confirmed by a sufficiently sized trial. Therefore, the debate over the optimal formula for IOL power selection in short eyes still persists. The present meta-analysis aimed to compare the
accuracy of different formulas in predicting IOL power in the patient with short AL and provide a clinical suggestion for IOL power selection in short eyes.

METHODS

Literature Search
Two independent investigators (W.Q and J.W) conducted the electronic databases (Pubmed, EMBASE, Cochrane Data Base of Systematic Reviews and the Cochrane Central Register of Controlled Trials) search on October, 2016 using the search term: (calculat*OR formula*) AND (microphthalmos OR nanophthalmos OR short axial length OR short axial lengths OR hyperopi* OR small eye*) AND (cataract OR IOL). The two authors evaluated the title and abstract of all the studies found and also checked the reference lists of all the included studies for eligibility.

Inclusion and Exclusion Criteria
Inclusion criteria for studies were: (1) eyes with AL less than 22.00mm, (2) eyes undergoing uncomplicated cataract or clear lens extraction and IOL implantation, (3) at least two types of the target IOL power calculation formula (Haigis, Hoffer Q, Holladay 1, Holladay 2, SRK/T, SRK II) used, (4) AL measured by partial coherence interferometry (PCI). Exclusion criteria for studies were: (1) patients with a prior history of disease affecting refraction or corneal refractive surgery, (2) multifocal, toric, piggyback or not in-the-bag fixated IOL implantation, (3) MAE data unavailable.

Data Extraction and Quality Assessment
Two pairs of authors (W.Q. and L.T.; J.W. and W.X.) extracted data independently and compared the result. The discrepancy was resolved by conferring results with a third author (L.H.). We assessed the quality of evidence by using a modified check-list adapted from the QUADAS-2 tool\textsuperscript{21, 22}. Study characteristics extracted from the retrieved studies were sample size, demographic data (age, sex, axial lengths, anterior chamber depth and corneal power), the formula used and its MAE, the IOL
type, and the postoperative refraction time and method. We used the MAE and standard deviation (SD) data from trials whenever possible. If the datum is not reported, we calculated it from the raw data provided by the studies. If the SD data cannot be retrieved from the text, we used the mean SD of the remaining studies.

**Statistical Analysis**

The target outcome was the MAE of each formula. We used the MAE rather than prediction error (PE) to circumvent the situation that positive/negative PE will be canceled out by negative/positive PE\(^{10}\). MAE was defined as the average of the absolute PE value. And PE was back-calculated by subtracting the postoperative refraction from the predicted refraction produced by each formula. We used weighted mean difference (WMD) to analyze the continuous outcome data (MAE) and \(I^2\) to estimate the statistical heterogeneity. An \(I^2\) value greater than 50% was considered as substantial heterogeneity. In this case, the random-effect model analysis was performed. Otherwise, the fixed-effect model was applied. We also conducted sensitivity analysis and subgroup analysis to evaluate the change in overall effect when the \(I^2\) value was greater than 50%. We performed funnel plots and egger’s test to test the publication bias and small-study effect too. Trim-and-fill analysis\(^{23}\) will be performed to assess the stability if asymmetrical plots appeared. Data pooling was done by using Review Manager 5.0 and STATA 14.0.

**RESULTS**

Literature search initially identified 818 articles (Fig. 1). After duplicates removal, 600 records were left, of which 560 records were considered irrelevant. 40 studies were selected for full-text assessment. Among them, 9 trials included only one types of the target IOL power calculation formulas, 8 trials used ultrasound method to measure AL, 7 trials did not have MAE data, 6 trials included eyes with AL larger than 22.0mm and the individual qualified data could not be extracted.
Figure 1: Flowchart of trial selection.

Study characteristics

In total, there are 1161 eyes are enrolled from the 10 included studies (Characteristics shown in Table 1). The sample size ranged from 15-608 eyes. All of the trials utilized IOL master for AL measurement. The majority of the studies (n=8) included patients undergoing cataract surgeries, 1 trial included patients undergoing refractive lens exchange and 1 trial was unclear.
Table 1: Characteristics of study participants

<table>
<thead>
<tr>
<th>Author/Years</th>
<th>Patients/Eyes</th>
<th>Gender</th>
<th>Mean age±SD/Range (Y)</th>
<th>AL(mm) SD/Range</th>
<th>IOL</th>
<th>Post-op refraction</th>
<th>Surgery Method</th>
<th>Refraction Method</th>
<th>Haigis</th>
<th>Hoffer Q</th>
<th>Holladay 1</th>
<th>Holladay 2</th>
<th>SRK/T</th>
<th>SRK II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haigis 2007</td>
<td>NA/31</td>
<td>NA</td>
<td>NA</td>
<td>21.44±0.58</td>
<td>SA60AT</td>
<td>NA</td>
<td>Cataract</td>
<td>NA</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gavin 2008</td>
<td>41/41</td>
<td>NA</td>
<td>NA</td>
<td>21.51 (20.29~21.96)</td>
<td>MA60</td>
<td>2-3W</td>
<td>Cataract</td>
<td>objective</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terzi 2009</td>
<td>11/19</td>
<td>4/7</td>
<td>53±7 (43-62)</td>
<td>21.24±0.55 (20.13-21.97)</td>
<td>AR40e: SA60AT</td>
<td>1M</td>
<td>RLE subject</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roh 2011</td>
<td>17/25</td>
<td>1/16</td>
<td>70.6±5.5 (61-80)</td>
<td>21.60±0.41 (20.41-21.94)</td>
<td>AR40e: MI60; ZA9003</td>
<td>2M</td>
<td>Cataract</td>
<td>objective</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2012</td>
<td>97/163</td>
<td>NA</td>
<td>57±10 (33-82)</td>
<td>21.2±0.60 (19.23-21.98)</td>
<td>AO/Adapt/</td>
<td>5.3W</td>
<td>NA</td>
<td>objective</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Srivannaboon 2013</td>
<td>NA/15</td>
<td>NA</td>
<td>NA</td>
<td>21.44 (18.77-21.94)</td>
<td>ACR6D/L302-1 (2-17.7W)</td>
<td>3M</td>
<td>Cataract</td>
<td>subjective</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eom 2014</td>
<td>75/75</td>
<td>5/70</td>
<td>70.1±6.8 (52-85)</td>
<td>21.69±0.29 (20.32-21.99)</td>
<td>Acrysof IQ</td>
<td>3-10w</td>
<td>Cataract</td>
<td>objective</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carifi 2015</td>
<td>28/28</td>
<td>11/17</td>
<td>72±10 (55-92)</td>
<td>19.86±0.55 (18.41-20.64)</td>
<td>SA60AT</td>
<td>&lt;4W</td>
<td>Cataract</td>
<td>subjective</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kane 2016</td>
<td>156/156</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>SN60WF</td>
<td>2W</td>
<td>Cataract</td>
<td>subjective</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA not available; Y year; M male; F female; SD standard deviation; RLE refractive lens exchange
Methodological Quality of Included Studies

The summary of quality assessment with the modified QUADAS-2 is presented in Fig. 2 and full assessments for each study are provided in Appendix 1. For patient selection, the majority of the studies didn’t report whether the enrollment of the patients was consecutive or random, and therefore, had an unclear degree of risk of bias. For accounting for all the patients, index test, and flow assessment, most of the studies were of high quality.

Figure 2: Quality assessment of the included trials based on modified QUADAS-2.

Outcomes

In total, 1161 eyes are enrolled, of which there are 218 with Holladay 2, 512 with Haigis, 1161 with Hoffer Q, 986 with Holladay 1, 1071 with SRK/T and 84 with SRK II. The overall MAEs of each of the above formulas is 0.496D, 0.498D, 0.510D, 0.513D, 0.555D and 1.146D respectively (Fig. 3A).

Figure 3: The overall MAE and standard error of each included formulas (A) and the forest plots for the analysis of MAE introduced by different formulas. (B) The MAE introduced by Haigis and Holladay 2. (C) The MAE introduced by Haigis and Hoffer Q. (D) The MAE introduced by Haigis and Holladay 1. (E) The MAE introduced by Haigis and SRK/T. (F) The MAE introduced by Haigis and SRK II.
The $I^2$, mean difference and 95% confidence interval is shown in table 2. By pairwise comparison, substantial heterogeneity was only detected in 5 pairs (Table 2) and the random-effect model was chosen in this case. Among them, the statistical heterogeneity was detected from the comparison between Haigis and SRK II (Fig. 3F, $X^2=8.29$, df=2, $p=0.02$, $I^2=76\%$). The sensitivity analysis showed that $I^2$ decreased to 35% ($p=0.21$, data not shown) without significantly altering the overall result by omitting Carifi 2015. Subgroup analysis further confirmed that significant difference existed between Carifi 2015 and the other two trials ($P=0.009$, data not shown). Neither funnel plot nor egger's test detected statistical finding ($P>0.05$, data not shown).

The comparisons between Haigis and the other formulas are listed in Fig. 3B-F. Haigis introduced significantly smaller MAE to the eyes than Hoffer Q (Fig. 3C, $p=0.003$). The mean difference (95% confidence interval, CI) was $-0.07\text{D} (-0.12\text{D} to -0.02\text{D})$. Haigis
also brought significantly smaller MAE than SRK/T and SRK II, with -0.07D (-0.13D to -0.02D) and -0.41D (-0.73D to -0.09D) mean difference (95%CI) respectively (Fig. 3E, F). For the remaining pairwise comparisons, the differences between formulas are not significant (Appendix 2).

Table 2: Pooled estimates with 95% confidence interval

<table>
<thead>
<tr>
<th>Formula 1</th>
<th>Formula 2</th>
<th>No. Studies</th>
<th>Eyes</th>
<th>$I^2$ (%)</th>
<th>Model used</th>
<th>mean difference</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haigis</td>
<td>Holladay 2</td>
<td>4</td>
<td>218</td>
<td>0</td>
<td>Fixed</td>
<td>-0.01</td>
<td>-0.08,0.06</td>
<td>0.86</td>
</tr>
<tr>
<td>Haigis</td>
<td>Hoffer Q</td>
<td>8</td>
<td>512</td>
<td>39</td>
<td>Fixed</td>
<td>-0.07</td>
<td>-0.12,-0.02</td>
<td>0.003*</td>
</tr>
<tr>
<td>Haigis</td>
<td>Holladay 1</td>
<td>4</td>
<td>378</td>
<td>0</td>
<td>Fixed</td>
<td>-0.03</td>
<td>-0.09,0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>Haigis</td>
<td>SRK/T</td>
<td>6</td>
<td>422</td>
<td>7</td>
<td>Fixed</td>
<td>-0.07</td>
<td>-0.13,-0.02</td>
<td>0.009*</td>
</tr>
<tr>
<td>Haigis</td>
<td>SRK II</td>
<td>3</td>
<td>84</td>
<td>76</td>
<td>Random</td>
<td>-0.41</td>
<td>-0.73,-0.09</td>
<td>0.01*</td>
</tr>
<tr>
<td>Holladay 2</td>
<td>Hoffer Q</td>
<td>4</td>
<td>218</td>
<td>0</td>
<td>Fixed</td>
<td>0.03</td>
<td>-0.10,0.04</td>
<td>0.38</td>
</tr>
<tr>
<td>Holladay 2</td>
<td>Holladay 1</td>
<td>2</td>
<td>184</td>
<td>32</td>
<td>Fixed</td>
<td>0</td>
<td>-0.11,0.11</td>
<td>0.97</td>
</tr>
<tr>
<td>Holladay 2</td>
<td>SRK/T</td>
<td>3</td>
<td>203</td>
<td>57</td>
<td>Random</td>
<td>-0.06</td>
<td>-0.21,0.09</td>
<td>0.43</td>
</tr>
<tr>
<td>Holladay 2</td>
<td>SRK II</td>
<td>1</td>
<td>28</td>
<td>NA</td>
<td>Fixed</td>
<td>-1.2</td>
<td>-1.74,-0.66</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Hoffer Q</td>
<td>Holladay 1</td>
<td>5</td>
<td>986</td>
<td>0</td>
<td>Fixed</td>
<td>0</td>
<td>-0.05,0.04</td>
<td>0.87</td>
</tr>
<tr>
<td>Hoffer Q</td>
<td>SRK/T</td>
<td>8</td>
<td>1071</td>
<td>19</td>
<td>Fixed</td>
<td>-0.01</td>
<td>-0.05,0.02</td>
<td>0.48</td>
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<tr>
<td>Hoffer Q</td>
<td>SRK II</td>
<td>3</td>
<td>84</td>
<td>90</td>
<td>Random</td>
<td>-0.35</td>
<td>-0.84,0.14</td>
<td>0.16</td>
</tr>
<tr>
<td>Holladay 1</td>
<td>SRK/T</td>
<td>5</td>
<td>986</td>
<td>0</td>
<td>Fixed</td>
<td>-0.03</td>
<td>-0.07,0.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Holladay 1</td>
<td>SRK II</td>
<td>2</td>
<td>59</td>
<td>79</td>
<td>Random</td>
<td>-0.56</td>
<td>-1.24,0.12</td>
<td>0.11</td>
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<tr>
<td>SRK/T</td>
<td>SRK II</td>
<td>3</td>
<td>84</td>
<td>61</td>
<td>Random</td>
<td>-0.19</td>
<td>-0.46,0.08</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* P<0.05; CI confidence interval, NA not available

DISCUSSION

MAE, defined as the average of the absolute PE value, is an effective indicator in determining the accuracy of the IOL power calculation formulas. A smaller MAE is related to better postoperative uncorrected visual acuity, and therefore, lower incidence of litigations after IOL implantations. This meta-analysis investigated the accuracy of different IOL power calculation formulas in eyes with short AL by measuring MAE. The results indicate that Haigis is superior to Hoffer Q, SRK/T, and
SRK II with statistical significance in accordance to some of the previous reports\textsuperscript{16, 17, 26}. However, no statistical difference between Haigis and Holladay 1 and Holladay 2 was identified. Furthermore, the largest MAE difference is reached between Holladay 2 and SRK II (0.65D).

The IOL power calculation in eyes with short AL is more problematic than the ones with normal or long AL\textsuperscript{3, 21}. The special anatomic characteristics and the high IOL power needed in short eyes might account for the difficulties in achieving precise prediction. An early study suggested that errors of IOL power calculation were attributed to incorrect axial length measurement (54%), postoperative ACD estimation (38%) and corneal power evaluation (8%)\textsuperscript{28}. Additionally, Hoffer\textsuperscript{3} found slight errors in predicted effective lens position (ELP) was related to dramatic postoperative refraction error in short eyes when the IOL power was high. Maclaren\textsuperscript{29} indicated that ELP didn't have much impact on the postoperative refraction error in high myopic eyes implanted with zero or negative-powered IOLs. Furthermore, Maclaren inferred that the high IOL power, thick IOL, was a crucial factor affecting postoperative refraction in short eyes\textsuperscript{16}.

In order to control the heterogeneity and bias, the present analysis not only excluded the patients with AL larger than 22mm but also excluded the studies which performed their biometric measurement using devices other than IOL master. The accuracy in AL measurements is a crucial parameter in predicting IOL power. Roy indicated that there was a significant difference in AL measurements between PCI and ultrasound biometry (UB)\textsuperscript{30}, and the former showed superiority in predicting IOL power\textsuperscript{31, 32}. As a result, PCI has been performed as standard procedure for over a decade and chosen in our analysis. Additionally, this meta-analysis considered an $I^2$ value greater than 50\% as substantial heterogeneity. In this case, we calculated the weighted mean differences with random effect model to achieve a relatively conservative result. Furthermore, sensitivity analysis and subgroup analysis were conducted. Both of the analysis for the comparison between Haigis and SRK II indicated that the
heterogeneity might result from the difference between Carifi 2015 and the other two studies. However, for IOL type, Carifi 2015 and Haigis 2007 both used SA60AT. For IOL constant optimization, neither Carifi 2015 nor Roh 2011 was personalized. For the postoperative time of performing refraction, Carifi 2015 and Roh 2011 both performed refraction before 3 months postoperatively. Therefore, all the above factors may not be the source of heterogeneity. By observing the AL from the included studies, we found that Carifi 2015 reported potentially shorter AL (19.86±0.55, 18.41-20.64) than the other two trials. However, since the individual data were unavailable, comparison of the AL among the three trials cannot be performed. Therefore, it still needs to be further verified that the heterogeneity was caused by the AL difference. For refraction method, Carifi 2015, Roh 2011 and Haigis 2007 used subjective, objective and unknown refraction respectively. The refraction method difference might be also a source of heterogeneity. The subgroup analysis on refraction method showed that the difference is statistically significant (P=0.007, Appendix 3) in the comparison between Haigis and SRK II. However, there was no significant subgroup difference among the other formulas. For the correction factors in the computation of optimized formulas, due to the limitation of the information provided from the original studies, subgroup analysis cannot be performed. However, we calculated the weighted mean differences with random effect model to achieve a relatively conservative result and avoid false positive results. Moreover, due to the limitation in the sample size of the included studies, the heterogeneity of the comparison might be overestimated. With incorporating more studies, the heterogeneity might be reduced or the source of heterogeneity might be found.

In the present study, Haigis performed better than Hoffer Q, SRK/T and SRK II. A possible explanation for the result is that Haigis involved three constants (a0, a1 and a2) and 2 parameters (ACD and AL) in predicting the ELP, the distance from the secondary principal plane of the cornea to the principal plane of the thin-IOL equivalent. Unlike Haigis, SRK II and SRK/T only use A-constant, a constant which is adjusted depending on the AL (SRK II) or AL and average keratometry (SRK/T) in
estimating ELP. Although Hoffer Q developed a personalized ACD to predict the pseudophakic ACD, ELP is still predicted based on AL. However, normal ACD is commonly seen in short eyes. In this case, personalized ACD will be underestimated.

In theory, since Holladay 2 incorporates additional biometric data (lens thickness, patient’s age, and preoperative refraction), ELP might be predicted more precisely and therefore, the IOL power estimation might be more accurate than other formulas. Similarly, Hoffer\textsuperscript{10} reported that Holladay 2 introduced smallest MAE after comparing it with the Hoffer Q, Holladay 1, and SRK/T in eyes with short AL. Additionally, Carifi and associates\textsuperscript{12} found Holladay 2 produced the smallest MAE among the 6 formulas compared in short eyes. However, the present analysis didn’t detect any statistically significant difference between Holladay 2 and other formulas. A potential explanation might be limited statistical power due to the small sample sizes of Holladay 2. Therefore, further study is needed for comparison among Haigis, Holladay 2, and Holladay 1.

The current analysis had limitations. (1) There was variability in the selection criteria of individual trials, including the patients’ characteristics, IOL types, capsulorhexis size and surgical techniques. (2) The sample size in some groups is small and therefore reduced the precision of the pooled estimates. (3) UB is still needed in the patients with dense vitreous opacities or cataracts. Since the result of this analysis was obtained from studies with IOL master measurement, the application of this result in the patients with UB measurement is not recommended.

There are a variety of formulas in estimating IOL power in patients with short AL. According to our result, among the formulas compared, Haigis produces more accurate prediction than Hoffer Q, SRK/T, and SRK II. Except for Holladay 1 and Holladay 2, which need to be further compared with Haigis by a methodologically sound and a sufficiently sized trial, Haigis is recommended in IOL power calculation for short eyes.
REFERENCES


12. Carifi G, Aiello F, Zygoura V, et al. Accuracy of the refractive prediction determined...


