A comparative study on endothelial cell loss in nanophthalmic eyes undergoing cataract surgery by phacoemulsification

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Purpose: The purpose of this study is to compare the endothelial cell loss (ECL) in nanophthalmic eyes and age-matched controls undergoing cataract surgery by phacoemulsification and also to identify the risk factors influencing the endothelial cell density (ECD). This was a prospective comparative interventional case series. Methods: We enrolled 19 nanophthalmic eyes (study group) and 42 age-matched cataract controls (control group) undergoing phacoemulsification after meeting the inclusion criteria. Ocular parameters like best-corrected visual acuity, intraocular pressure, pachymetry, specular microscopy, and slit lamp findings were noted preoperatively and at month 1 and 3 postsurgery. All nanophthalmic eyes underwent cataract surgery with concomitant prophylactic posterior sclerostomy. Results: The median percentage endothelial loss in nanophthalmic eyes was 4.0 (IQR 0–23.5), 7.4 (IQR 1.0–22.4) at 1 and 3 months postoperatively compared to 6.3 (IQR 1.7–14.1) and 6.4 (IQR 2.6–12.1) in age controlled normal eyes ($P = 0.94$, $P = 0.46$, respectively). Linear regression analysis showed increasing age as the only variable influencing the percentage decrease in corneal ECD in the study group ($P = 0.001$). Nanophthalmic eyes with ACD <2.5 mm had a significantly greater reduction in ECD at 3 months postcataract surgery compared to baseline ($P = 0.039$). Visual outcomes and IOP reduction in the study group with ACD >2.5 mm were significantly better postcataract surgery ($P = 0.02$ and $P = 0.002$, respectively). Conclusion: The percentage of ECL in nanophthalmic eyes undergoing phacoemulsification is equivalent to normal eyes. However, in the nanophthalmic eyes with AC depth <2.5 mm, the percentage cell loss was significantly higher warranting the need for extensive intraoperative care. Increasing age was found to be the only significant risk factor influencing the ECD in short eyes.

Key words: Corneal endothelial cell, nanophthalmos, phacoemulsification

The spectrum of small eye phenotypes comprises of a global reduction in axial length or shortening of either the anterior or posterior segment. In nanophthalmos, the anterior and posterior segments have no other congenital anomalies but are both reduced in size, with increase in retino-choroidal-scleral thickness.[11] Nanophthalmic eyes have a high incidence of angle-closure glaucoma and spontaneous uveal effusion syndrome and fraught with postoperative complications such as malignant glaucoma, corneal decompensation, retinal and choroidal detachment, and vitreous hemorrhage.[2-4] Nanophthalmos is a rare entity with a prevalence of 0.0009% in the Asian population and 0.002–0.017% in the British population,[6,7] and its surgical management presents a significant clinical challenge.

Advances in phacoemulsification and intraocular lenses (IOLs) have shown encouraging results in nanophthalmic eyes undergoing cataract surgery.[8-11] Performing a simultaneous prophylactic posterior sclerostomy along with cataract surgery has proven to reduce intraoperative complications in short eyes.[10] Corneal decompensation is rare but a potentially vision-threatening complication after phacoemulsification surgery. Evaluation of the preoperative, intraoperative, and postoperative risk factors in nanophthalmic eyes may provide useful information to the cataract surgeon in dealing with this complication. Prior studies have reported old age, dense cataract, high ultrasound energy, prolonged phacoemulsification time, faulty phacoemulsification technique, and large infusion volumes to increase the risk of endothelial cell loss (ECL) after phacoemulsification in nanophthalmic eyes.[12-16]

This study was undertaken to evaluate the ECL after phacoemulsification in nanophthalmic eyes versus age-matched controls and also to identify the associated risk factors for the cell loss in these eyes.

Methods

This prospective study was approved by the institutional ethics committee and was conducted as per the tenets of the

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In our study, nanophthalmos was diagnosed based on axial length less than 20.5 mm and retina-choroidal-scleral (RCS) thickness more than 1.7 mm on B-scan ultrasonography. We included nanophthalmic eyes with visually significant cataract, anterior chamber depth (ACD) more than 1.5 mm, and cataract grade less than nuclear opalescence (NO) grade 5 as per lens opacities classification system III (LOCS III).[16] Exclusion criteria were any associated anatomic and structural abnormalities like microcornea, chorioretinal coloboma, retinitis pigmentosa or foveal schisis, eyes requiring treatment beyond cataract surgery, such as trabeculectomy, those with history of previous ocular trauma or inflammation, corneal pathology, endothelial cell counts <2000 cells/mm² and eyes with corneal diameter less than 11 mm in view of excluding relative anterior microphthalmos. A control group of 42 normal eyes with visually significant cataract less than NO grade 5 as per LOCS III was included.

Preoperative evaluation

All enrolled patients underwent a detailed ophthalmic evaluation by clinicians and trained technicians masked to study data, and the parameters recorded were best-corrected visual acuity (BCVA) measured by Snellen visual acuity charts, manifest refraction using auto-refractometer (Auto-Ref-Keratometer, RK-5; Canon, Tokyo, Japan) confirmed with clinical refraction, slit lamp examination (Haag Streit, USA) [Fig.1a] for anterior segment evaluation and cataract grading using LOCS III grading system; fundus examination for disc parameters and other posterior segment pathology using an indirect 90D Volk lens. Intraocular pressure (IOP) measurement using Goldmann applanation tonometry (GAT), Zeiss four mirror prism gonioscopy (for Shaffer grading), corneal diameter measurement (by slit lamp), and central corneal thickness (CCT) measurement by pachymetry (Pacscan300 AP, digital biometric ruler, Ascon, Sonomed, NY, USA). All patients underwent preoperative fitness-for-surgery evaluation by the in-house general physician with more than 15 years’ experience. All eyes in the nanophthalmos group underwent laser peripheral iridotomy (LPI) (Visulas YAG II plus, Carl Zeiss, Oberkochen, Germany) minimum 2 weeks before the cataract surgery and specular microscopy was done as part of the study protocol, one day before surgery. After LPI, cataracts were graded postdilatation using the LOCS III grading system and fundus examination was repeated. Axial length, ACD, lens thickness, and IOL power values were obtained using the IOL Master (Carl Zeiss Meditec AG, Germany). Hoffer Q formula was used for IOL power calculation based on previous experience.[19] Eyes were stratified into two groups ACD I, >1.5 to ≤2.5 mm and ACD II, >2.5 to ≤3.5 mm based on a study by Hwang HB et al. who found a significant ECL in eyes with ACD ≤2.5 mm undergoing phacoemulsification.[18] All nanophthalmos eyes underwent B-scan ultrasonography (OTX, Biomedics, USA) preoperatively to rule out the presence of uveal effusion and to measure the RCS thickness [Fig.1b].

Specular microscopy

To evaluate central corneal endothelial cell density (ECD), specular microscopic photographs of the central corneal endothelium were taken using a noncontact specular microscope (Konan noncon robo; Konan Medical Inc., Hyogo, Japan) in automatic mode. Three photographs were taken for each eye, and the “Center method” of Konan specular microscope was used to obtain the ECD from the best quality image obtained, as followed previously in similar research.[16] Corneal ECL was evaluated by measuring the percentage decrease in ECD of the central cornea (cells/mm²). The percentage decrease in central corneal ECD was expressed as (preoperative central corneal ECD – postoperative central corneal ECD) ×100/preoperative central corneal ECD.

Surgical procedure

All procedures were performed by the same surgeon (RS) using subtenon anesthesia. All the nanophthalmic eyes underwent prophylactic posterior sclerostomy in the inferotemporal quadrant before phacoemulsification in the same sitting. All controls underwent standard phacoemulsification technique. To describe the standard phacoemulsification technique, a 2.8 mm clear corneal incision was made in the temporal quadrant. A capsulorhexis approximately 5.0 mm in diameter was created with forceps, and then cortical cleaning hydrodissection was performed. The nucleus was emulsified by centurion vision system (Alcon Laboratories Inc., Fort Worth, TX U.S.A) using the stop and chop technique. After irrigation and aspiration of the cortex, a foldable acrylic IOL (SN60WF; Alcon Laboratories Inc., Fort Worth, TX, USA) was implanted in the bag. The same type of irrigating solution (balanced salt solution, BSS) and the same type of ophthalmic viscosurgical device (OVD, sodium hyaluronate 1.2%) were used for all patients. Surgery time was recorded starting from creating the side port to the end of stromal wound hydration. Effective phaco time, cumulative dissipative energy (CDE) and any complications were recorded.

Postoperative follow-up

All the patients underwent postoperative work up including BCVA, IOP, CCT, and specular microscopy of the central corneal endothelium using a noncontact specular microscope at postoperative month 1 and month 3 and were compared with the baseline in both the groups.

Statistical analysis

The characteristics observed are presented as mean ± SD for normally distributed continuous variables and as rates for categorical data. The distribution of data was evaluated using Shapiro-Wilk test and box-plot. Percentage decreases in ECD were compared using independent t-test according to the ACD group (<2.5 and >2.5 mm); postoperative comparison of ECD was made using paired t-test. Categorical variables were compared using the Chi-square test. Simple linear regression analysis was used to analyze the relationship between ECD and age, axial length, RCS, lens thickness, BCVA, IOP, pachymetry, and ACD. Data were entered into Microsoft Excel, and all data were analyzed using STATA (version 14.0, Texas, USA) statistical analysis software package and P value <0.05 was considered significant.

Results

A total of 26 eyes of 20 nanophthalmos patients underwent phacoemulsification in the study duration. Nineteen eyes of
15 patients meeting the inclusion criteria were enrolled in the study group and the control arm included 42 eyes of 21 age-matched patients. The baseline demographics and clinical characteristics are shown in Table 1.

The study eyes were further analyzed based on the ACD with a cut off value of 2.5 mm. In the study group, the mean ACD was 2.82±0.94 (95% CI) mm. Eyes with ACD >2.5 mm (n = 10) showed significantly lower ECD changes & ECL compared to eyes with ACD <2.5 mm (n = 9) (P = 0.039). They also had significantly better visual outcomes and lower IOP levels at 3 months post surgery, compared to eyes with ACD <2.5 mm [Table 2].

ECD changes between the study & control groups did not show any significant difference postoperatively [Table 3]. However, there was a difference between the baseline & postoperative BCVA and IOP in both the groups, with the control group having better visual acuity & IOP reduction [Table 3].

The surgical time between the two groups significantly differed (P < 0.001), with less operating time in the control group (mean 9.83±2.40 min, median 10.0 [IQR 10–10]) than the nanophthalmos group (mean 21.0±16.20 min, median 15.0 [IQR 10–25]). The time taken for scleral window creation (10–15 min) in the study group was not included in the analysis. Despite the difference in the surgical time between the two groups, the comparison of the percentage of ECD loss between the two groups at month 1 and 3 showed no significant difference (P = 0.94 and P = 0.46, respectively). Also, the CDE between the two groups failed to show a statistically significant difference (P = 0.266) [Table 3].

Comparison of the ECD values in eyes which required CDE ≤7% sec and those which required more than 7% sec did not show any statistical difference between the two groups as shown in Table 4.

Analysis of the various risk factors (age, axial length, RCS thickness, lens thickness, phaco time, ACD, CCT, IOP, and BCVA) associated with ECD changes between the study & control groups using linear regression analysis showed age as the only statistically significant contributing factor in the study group (P-value = 0.001) [Table 5].

One eye in the study group (5.3%) presented with malignant glaucoma at 1-month postsurgery. Biometric evaluation of this patient had an axial length of 15.6 mm, ACD 1.6 mm, lens thickness 4.9 mm, RCS thickness of 2.05 mm, and patent peripheral iridotomy. A single-piece + 40.0D IOL was implanted. However, the intraoperative course was longer; surgical time was 55 min with cumulative dissipated energy of 3.06% s. This patient underwent pars plana vitrectomy after 1 month. Given the repeat surgery, this eye was removed from

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Table 1: Baseline demographics and clinical characteristics of patients

| Variable | Mean (SD) | 95% CI or % | P* |
|----------|-----------|-------------|----|
| Age      |           |             |    |
| Study group | 52.3 (14.4) | 44.4–60.3 | 0.187 |
| Control group | 56.9 (5.5) | 54.5–59.4 |    |
| Gender (n, %men) | | | |
| Study group | 4 | 26.7% | 0.319^ |
| Control group | 9 | 42.9% |    |
| Preoperative BCVA (LogMAR Median) | | | |
| Study group | 0.78 (6/36) | 0.48–1.00* | <0.001^ |
| Control group | 0.30 (6/12) | 0.30–0.48 |    |
| Preoperative IOP (mmHg) | | | |
| Study group | 17.3 (4.8) | 14.9–19.6 | 0.018 |
| Control group | 14.7 (3.2) | 13.7–15.7 |    |
| Endothelial cell density | | | |
| Study group | 2688.1 (406.1) | 2492.3–2883.9 | 0.569 |
| Control group | 2730.6 (176.7) | 2675.5–2785.7 |    |
| CCT | | | |
| Study group | 460.1 (49.5) | 436.2–484.0 | 0.459 |
| Control group | 452.7 (28.1) | 443.9–461.4 |    |
| Axial length | | | |
| Study group | 18.6 (1.8) | 17.7–19.5 | <0.001 |
| Control group | 23.0 (0.5) | 22.9–23.2 |    |
| Diabetes, n (%) | | | |
| Study group | 3 | 20.0% | >0.99^ |
| Control group | 4 | 19.1% |    |
| Cataract grade ¥ , n (%) | | | |
| Soft | | | |
| Study group | 15 | 41.7% | 0.033^ |
| Control group | 21 | 58.3% |    |
| Hard | | | |
| Study group | 4 | 16.0% |    |
| Control group | 21 | 84.0% |    |

*Independent t-test, ^Chi-square test, \*Mann-Whitney U test, ¥Interquartile range, ¥Cataract grade divided as per LOCS III, Soft grade: ≤ Nuclear Opalescence (NO) 2; Nuclear Color (NC) 2, ¥Posterior Subcapsular Cataract (P) 3, ¥Cortical cataract (C) 2, Hard grade ≥ NO/NC, ≥ P4, ≥ C3. BCVA – best-corrected visual acuity, CCT – central corneal thickness
all the postoperative analyses. None of the other eyes was noted to have any complications requiring reintervention or close monitoring.

**Discussion**

Corneal endothelial changes after phacoemulsification are important prognostic factors to assess the visual outcomes in patients with nanophthalmos undergoing cataract surgery. We report the results of ECD changes in nanophthalmic eyes versus age-matched controls. The overall ECL was 7.4% in the nanophthalmos group and 6.4% in the control group at 3 months postcataract surgery.

Interestingly, in the nanophthalmic group, eyes with ACD less than 2.5 mm were noted to have a significant decrease in ECD compared to eyes with ACD >2.5 mm at the third post-op month ($P = 0.039$). This could possibly be attributed to the reduced surgical space in a shallow anterior chamber, the proximity of the phaco probe to the cornea, and generation of excess heat energy, causing a high risk of mechanical and thermal damage to the corneal endothelium.
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Table 4: Cumulative dissipated energy between the study and control group and the endothelial cell density comparison between eyes with CDE time ≤7% and >7% s

|                      | Study group (n=19) | Control group (n=42) | p   |
|----------------------|-------------------|----------------------|-----|
| Best-corrected visual acuity (BCVA) |                   |                      |     |
| Baseline             | Mean±SD 2736.6±478.8 | Mean±SD 2634.2±327.2 | 0.598 |
| Month 1              | Mean±SD 2451.4±514.4 | Mean±SD 2269.8±561.8 | 0.497 |
| Month 3              | Mean±SD 2491.2±801.5 | Mean±SD 2256.1±460.5 | 0.478 |
| Intraocular pressure (IOP) |                   |                      |     |
| Baseline             | Mean±SD 17.3±4.6 | Mean±SD 14.7±3.2 | 0.018 |
| Month 1              | Mean±SD 19.2±14.5 | Mean±SD 14.1±2.6 | 0.032 |
| Month 3              | Mean±SD 19.7±14.9 | Mean±SD 13.6±2.7 | 0.016 |
| Endothelial Cell Density (ECD) |                   |                      |     |
| Baseline             | Mean±SD 2688.1±406.1 | Mean±SD 2730.6±176.7 | 0.569 |
| Month 1              | Mean±SD 2421.6±525.3 | Mean±SD 2490.2±281.3 | 0.509 |
| Month 3              | Mean±SD 2448.9±651.5 | Mean±SD 2526.4±234.6 | 0.501 |
| Central corneal thickness (CCT) |                   |                      |     |
| Baseline             | Mean±SD 460.1±49.5 | Mean±SD 452.7±28.1 | 0.459 |
| Month 1              | Mean±SD 405.1±49.5 | Mean±SD 397.2±28.1 | 0.460 |
| Month 3              | Mean±SD 405.1±49.5 | Mean±SD 397.2±28.1 | 0.460 |
| Cumulative dissipated energy |                   |                      |     |
| Baseline             | Mean±SD 6.6 (4.6-13.5) | Mean±SD 5.9 (4.5-7.9) | 0.266 |
| Month 1              | Mean±SD 6.6 (4.6-13.5) | Mean±SD 5.9 (4.5-7.9) | 0.266 |
| Month 3              | Mean±SD 6.6 (4.6-13.5) | Mean±SD 5.9 (4.5-7.9) | 0.266 |

Table 3: Comparison of the clinical characteristics between the study and control group

|                      | Study group (n=19) | Control group (n=42) | p   |
|----------------------|-------------------|----------------------|-----|
| Best-corrected visual acuity (BCVA) |                   |                      |     |
| Baseline             | Mean±SD 0.78 (6/36) | Mean±SD 0.30 (6/12) | 0.30-0.48 | <0.001 |
| Month 1              | Mean±SD 0.48 (6/18) | Mean±SD 0.0 (6/6) | 0.0 | <0.001 |
| Month 3              | Mean±SD 0.30 (6/12) | Mean±SD 0.0 (6/6) | 0.0 | <0.001 |
| Intraocular pressure (IOP) |                   |                      |     |
| Baseline             | Mean±SD 17.3±4.6 | Mean±SD 14.7±3.2 | 0.018 |
| Month 1              | Mean±SD 19.2±14.5 | Mean±SD 14.1±2.6 | 0.032 |
| Month 3              | Mean±SD 19.7±14.9 | Mean±SD 13.6±2.7 | 0.016 |
| Endothelial Cell Density (ECD) |                   |                      |     |
| Baseline             | Mean±SD 2688.1±406.1 | Mean±SD 2730.6±176.7 | 0.569 |
| Month 1              | Mean±SD 2421.6±525.3 | Mean±SD 2490.2±281.3 | 0.509 |
| Month 3              | Mean±SD 2448.9±651.5 | Mean±SD 2526.4±234.6 | 0.501 |
| Central corneal thickness (CCT) |                   |                      |     |
| Baseline             | Mean±SD 460.1±49.5 | Mean±SD 452.7±28.1 | 0.459 |
| Month 1              | Mean±SD 405.1±49.5 | Mean±SD 397.2±28.1 | 0.460 |
| Month 3              | Mean±SD 405.1±49.5 | Mean±SD 397.2±28.1 | 0.460 |

A prospective study by Hwang HB et al., on ECD changes after phacoemulsification in different ACDs showed that cohort with ACD less than 2.5 mm had a significant ECL post-cataract surgery compared to eyes with ACD more than 2.5 mm.[18] Similarly in our study, we observed significant ECL in eyes with ACD less than 2.5 mm. However, Hwang HB et al. conducted the study on eyes with normal axial length and our study included nanophthalmic eyes.

The baseline IOP in our nanophthalmic cohort with shallow anterior chamber <2.5 mm was noted to be significantly higher, compared to eyes with ACD >2.5 mm (P = 0.047). The higher IOP may also have attributed to higher ECL in this group as per previous reports.[18] Loss of corneal endothelial function by surgical damage may compromise the endothelial pump mechanism causing corneal decompensation, which is a potential vision-threatening complication after cataract
surgery. Earlier reports have shown several preoperative and intraoperative risk factors associated with ECL after phacoemulsification surgery like age, hard cataracts, high ultrasound energy, longer surgical time, and large infusion volumes.\(^\text{[12-16]}\)

Our study identified patients’ age as a significant risk factor for ECD changes post-cataract surgery in the nanophthalmic eyes on multiple regression analysis (\(P = 0.001\)). Varadaraj V \textit{et al.} in their study on eyes with shallow anterior chamber, has also shown age as a risk factor for increased ECL.\(^\text{[18]}\) Several authors have shown a decrease in ECD with increasing age with a 0.3–1% loss of endothelial cells every year in various populations.\(^\text{[16]}\) Like every tissue of the human body, the corneal endothelium undergoes age-related changes, with a reduction in ECD and loss of endothelial pump function and thus one may need to follow them for a longer period following cataract surgery.

We observed a significant difference in the surgical time between the study and the control group. In the nanophthalmic group, though the surgical time was longer due to the complexity of the cases involved, we could not identify its association with the ECD on regression analysis. This could possibly be due to the single experienced surgeon performing all surgeries, operating with modern phacoemulsification machine and liberal use of ophthalmic viscosurgical devices intraoperatively.

Previously, Day \textit{et al.} evaluated the outcomes of phacoemulsification and IOL implantation in 63 microphthalmos and nanophthalmos eyes and had reported 47.6% with major complications, such as malignant glaucoma, zonular dehiscence, and severe uveitis.\(^\text{[11]}\) However, we had a low complication rate (5.3%) in our series, which could possibly be due to the concomitant prophylactic posterior sclerostomy performed in all our study eyes.

Major strengths of our study were the inclusion of normal patients undergoing cataract surgery as a control arm, and also by stratifying the ECL to various ACDs and a single surgeon performing all surgeries with a standard surgical technique.

The limitations of our study, however, include 1) small sample size. Larger sample size can give robust statistical outcomes. 2) The surgical parameters such as the tunnel length and the volume of irrigating solution used for each surgery could not be noted due to the complexity of the cases involved. 3) Early specular microscopy changes might have been missed as the cell size variation coefficient and percentage of hexagonality were not identified for analysis, 4) The reproducibility of similar results on ECL needs to be studied in nanophthalmic eyes undergo phacoemulsification without prophylactic sclerostomy. 5) Longer follow-up studies will be

| Table 5: Factors associated with ECD in nanophthalmic eyes undergoing cataract surgery using simple linear regression |
|---|---|---|---|---|
| Factor | Study group | | Control group | |
| | \(B\) coefficient (95% CI) | \(P\) | \(B\) coefficient (95% CI) | \(P\) |
| Age | -19.9 (-29.6 to -10.2) | 0.001 | 2.1 (-13.1 to 17.3) | 0.777 |
| Axial length | -39.1 (-147.9 to 69.7) | 0.458 | 38.6 (-73.0 to 150.2) | 0.489 |
| BCVA | -108.8 (-864.3-646.7) | 0.765 | 111.8 (-126.9-350.5) | 0.350 |
| IOP | 5.9 (-36.9 to 48.8) | 0.773 | 4.7 (-13.9 to 23.2) | 0.613 |
| Pachymetry | 1.8 (-2.3 to 5.9) | 0.371 | 1.2 (-0.8 to 3.2) | 0.230 |
| PHACO time | 5.8 (-6.7 to 18.3) | 0.340 | 5.4 (-18.1 to 28.8) | 0.647 |
| ACD* | -21.2 (-243.0 to 200.5) | 0.842 | - | - |
| RCS* | -223.9 (-845.7 to 397.9) | 0.458 | - | - |
| Lens thickness* | -87.8 (-221.7 to 46.1) | 0.185 | - | - |

*Factors ACD, RCS, lens thickness were analyzed only in the study group. BCVA – best corrected visual acuity, IOP – intraocular pressure, ACD – anterior chamber depth, RCS – retinochoroidoscleral

**Figure 1:**
(a) Slit lamp image showing peripheral shallow anterior chamber (white solid arrow mark) with patent laser peripheral iridotomy (white solid star mark) in a patient with nanophthalmos. (b) Ultrasound B scan showing increased retino-choroidal-scleral (RCS) thickness (white double arrow) measuring 2.3 millimeter in the same eye of the same patient.
required to assess the long-term changes in ECD values post cataract surgery in nanophthalmic eyes.

**Conclusion**

To conclude, the percentage of ECL in nanophthalmic eyes undergoing phacoemulsification was equivalent to age-matched cataract controls. However, in nanophthalmic eyes with AC depth <2.5 mm, the percentage cell loss was significantly higher warranting the need for extensive intraoperative care like maintaining the anterior chamber with a high molecular ophthalmic viscosurgical devices and meticulous tissue handling. Increasing age was found to be the only significant risk factor influencing the ECD in short eyes.

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**Conflicts of interest**

There are no conflicts of interest.

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