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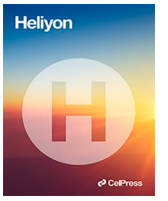

Research article

Proportion and risk factors of zonulopathy in patients with age-related cataract

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ABSTRACT

Purpose: To investigate the proportion of zonulopathy in patients with age-related cataract, and further explore demographics and ocular characteristics, as well as potential risk factors.
Methods: Hospital-based, observational, cross-sectional study. We enrolled consecutive patients who were 45 years or older and diagnosed with age-related cataract and underwent surgery between October 2022 and April 2023 at the Division of Cataract, Beijing Tongren Hospital. Zonulopathy was diagnosed based on intraoperative signs. We calculated the total proportion, age, and gender specific proportions of zonulopathy. We compared the demographic and ocular characteristics between the cases with and without zonulopathy. Univariate and multivariate logistic regression analyses were employed to determine the risk factors associated with the presence of zonulopathy in patients with age-related cataract.
Results: A total of 640 age-related cataract patients with a median age of 70.0 (64.0–77.0) were enrolled. Zonulopathy was diagnosed intraoperatively in 70 patients (10.9%). Compared with the patients having no zonulopathy, those with zonulopathy were likely to be older ($P < 0.001$), have a shallower central ACD ($P < 0.001$), a thicker lens ($P < 0.001$) and a shorter AL ($P = 0.010$). Logistic regression analyses showed that the risk predictors associated with the presence of zonulopathy in patients with age-related cataract were older age (OR, 1.042; $P = 0.035$) and shallower central ACD (OR, 0.834; $P < 0.001$).
Conclusion: Zonulopathy in age-related cataract patients is not an uncommon finding. Clinicians should be mindful of zonulopathy in patient population with advanced age and shallower ACD.

1. Introduction

Cataract, defined as opacification of the lens, is the most common cause of blindness, affecting an estimated 95 million people worldwide [1,2]. Age-related cataract is the most common type in adults, typically onset between the ages of 45–50 [2]. Advances in surgical techniques have made treatment highly effective and result in rapid visual recovery in most cases [1,2].

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With healthy zonule of Zinn appropriately supporting the lens, standard cataract surgery using phacoemulsification and aspiration combined with intraocular lens (IOL) implantation can be safely performed [3]. Zonulopathy, including zonular laxity and/or localized zonular dehiscence, is one of the complex conditions that can result in intraoperative and/or postoperative complications in cataract surgeries, including posterior capsular rupture, nucleus drop, vitreous prolapse, intraocular lens subluxation and dislocation [3,4]. Moreover, additional surgical management is often required in zonulopathy cases, including an adjunctive capsule stabilization device such as capsular tension ring (CTR) and changes in the surgical procedure [3]. In cases with severe zonulopathy, intracapsular cataract extraction, pars plana vitrectomy, or scleral suture fixation of IOL might be required [3,4].

Being aware about the presence of zonulopathy in advance can significantly assist with the surgeons and the patients in properly preparing the surgical plan and postoperative care, thereby improving the safety and vision outcome of surgery. Apparent zonulopathy can be diagnosed during the preoperative exam. However, diagnosing mild zonulopathy, zonular weakness, or subtle zonular dehiscence can be challenging. In our experience, mild to moderate zonulopathy in patients with age-related cataract is often revealed during surgery. Several intraoperative findings can serve as warning signs and be diagnostic. These include the wrinkling of anterior capsule during continuous curvilinear capsulorhexis (CCC), anterior capsule striae and/or instability of the lens complex during propagation of the capsular flap, the presence of lens equator with fully dilated pupil, and a deformed/decentered anterior capsulorhexis after nucleus/cortex removal [3,5].

In the present study, we aimed to investigate the proportion of primary zonulopathy in patients with age-related cataract and further explore the potential risk factors associated with zonulopathy in these patients. Furthermore, we anticipate that our findings could provide valuable information to help identify the at-risk population with zonulopathy in age-related cataract.

2. Material and methods

2.1. Participants

This was an observational, cross-sectional hospital-based study. We enrolled consecutive patients with age-related cataract aged 45 years or older, with an axial length of 21–26 mm from the Division of Cataract, Department of Ophthalmology at Beijing Tongren Hospital. All patients underwent phacoemulsification cataract extraction with intraocular lens implantation (CE + IOL) from October 2022 through April 2023. The diagnosis of age-related cataract was established by identifying any opacification caused by age-related changes, with a LOCS III grading of $\geq$2, with or without vision impairment [6,7].

The exclusion criteria included a past history of intraocular surgeries, laser peripheral iridotomy or iridoplasty, or ocular trauma; a past history of recorded intraocular pressure (IOP) rise due to angle closure; ocular diseases that may cause secondary zonulopathy, including pseudoexfoliation syndrome, choroidal detachment, retinal detachment, ciliary body detachment, intraocular tumor, spherophakia, Marfan's syndrome, homocystinuria, pigmentary degeneration of the retina, etc.; an axial length of $<$21 mm or $>$26 mm.

This study adhered to the tenets of the Declaration of Helsinki regarding research involving human participants. Written informed consent was obtained from all the participants, and the study was approved by the Ethics Committee of the Beijing Tongren Hospital (approval number: TREC2022-KY003).

2.2. Surgical procedure

All the cataract surgeries were performed by the same surgeon (X.D.S) under topical anesthesia. After creating the clear corneal main incision and paracenteses, an ample amount of ophthalmic viscosurgical device (OVD) was injected into the anterior chamber. CCC of the anterior lens capsule was performed using a capsulorhexis forceps, beginning with a puncture of the capsule in the center, then extending the tear and creating an anterior capsular flap, followed by gently pulling the flap with the forceps, and finishing the CCC of approximately 5.5 mm in diameter. Emulsification of the lens nucleus and aspiration of the lens cortex were then performed using INFINITI® Vision System (Alcon, Texas, USA). A foldable acrylic IOL was then implanted after the capsular bag was filled with an OVD. A CTR was used as needed in cases with zonular weakness or deficiency.

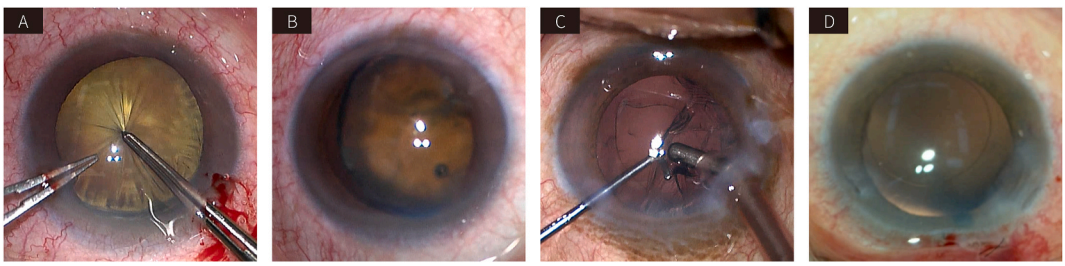

Fig. 1. Intraoperative Signs for Diagnosis of Zonulopathy
A. Wrinkling of lens anterior capsules during CCC; B. Presence of lens equator with fully dilated pupil; C. Infolding of peripheral capsule during cortical or nuclear removal; D. Decentation of anterior capsulorhexis after cortex removal.

2.3. Diagnostic criteria for zonulopathy

Intraoperative signs for the diagnosis of zonulopathy were as follows (Fig. 1A–D).

1) Wrinkling of lens anterior capsules with striae formation on the entire circumference surface during CCC with or without difficulty in performing CCC;
2) Presence of equator of the lens with fully dilated pupil;
3) Loose or floppy capsular bag, infolding of peripheral capsule or visualization of the capsular equator during the cortical or nuclear removal;
4) Out of shape or deviation of the anterior capsular opening after the cortex was removed.

Intraoperative sign (1) plus none or several of signs (2) to (4) were considered diagnostic of zonulopathy. Two senior ophthalmologists with more than 10 years of clinical experience of glaucoma practice (H.Z. and C.Y.Q.) independently evaluated the video footage during the surgery (operated by X.D.S) and documented the presence of zonulopathy in each eye. To evaluate the reliability of diagnosis, these two senior ophthalmologists independently assessed a group of 25 surgical videos with zonulopathy. Their diagnosis achieved a Kappa value of 0.918, which demonstrated excellent consistency. If there was a disagreement in zonulopathy diagnosis between the two ophthalmologists, the surgical videos were reviewed by another senior ophthalmologist with more than 10 years of clinical experience of glaucoma practice for final diagnosis.

2.4. Data collection

Demographics information and medical history were collected from each patient. Ocular examinations including Snellen visual acuity, IOP measurement, fundus photography, and IOL-Master 700 (Carl Zeiss Meditec, Jena, Germany) biometry measurement were performed before surgery. The Snellen visual acuity measurements were converted to logMAR format for comparison. The axial length (AL), anterior chamber depth (ACD) (incorporating central corneal thickness), and lens thickness (LT) were obtained by IOL-Master. The central ACD used for statistical analysis was calculated as ACD (obtained from IOL-Master) – central corneal thickness. The absolute lens position (ALP) was defined as central ACD + 1/2 × LT and the relative lens position (RLP) as ALP/AL.

2.5. Statistical analysis

We included the eyes of each patient who underwent the cataract surgery. For patients who had surgeries on both eyes, only the first operative eye was included. The total proportion of zonulopathy, age-specific, and gender-specific proportions of zonulopathy were calculated. Age was grouped into the following categories: 45–60 years, 61–70 years, 71–80 years, and >80 years. The Chi-squared test for trend was used to determine if the proportion of zonulopathy in patients with age-related cataract increased with increasing age. Statistical analysis was performed using SPSS statistical software (Version 25.0; SPSS, Inc., Chicago, IL, USA). All P values reported were two-tailed, and statistical significance was considered as $P < 0.05$.

Comparisons between patients with or without zonulopathy were performed, using *t*-test (normally distributed variables), Mann–Whitney *U* test (non-normally distributed quantitative variables), or $\chi 2$ test (qualitative variables). Univariate and multivariate

Table 1
Demographic and biometric characteristics in patients with age-related cataract combined with and without zonulopathy.

Parameter	Patients without Zonulopathy ($n = 570$)	Patients with Zonulopathy ($n = 70$)	*P* Value
Age (IR), y	69.5 (63.0, 76.0)	76.0 (68., 85.0)	<0.001[c]
Age group			
45–60 years (%)	112 (19.6)	6 (8.6)	<0.001[b]
61–70 years (%)	204 (35.8)	20 (28.6)	
71–80 years (%)	179 (31.4)	16 (22.9)	
>80 years (%)	75 (13.2)	28 (40.0)	
Sex			
Male (%)	24 (34.3)	224 (39.3)	0.417[b]
Female (%)	46 (65.7)	346 (60.7)	
PVA (IR)	0.52 (0.40, 1.00)	0.70 (0.40, 1.00)	0.899[c]
IOP (IR), mmHg	14.0 (12.3, 16.3)	13.7 (11.0, 16.3)	0.170[c]
Central ACD (SD), mm	2.51 (0.43)	2.19 (0.34)	<0.001[a]
LT (SD), mm	4.53 (0.48)	4.83 (0.43)	<0.001[a]
AL (IR), mm	23.40 (22.78, 24.19)	23.17 (22.56, 23.68)	0.010[c]
ALP (SD), mm	4.80 (0.32)	4.61 (0.26)	<0.001[a]
RLP (SD), mm	0.20 (0.12)	0.20 (0.01)	0.015[a]

SD, standard deviation; IR, interquartile range; PVA, presenting visual acuity, IOP, intraocular pressure; ACD, anterior chamber depth; LT, lens thickness; AL, axial length; ALP, absolute lens position; RLP, relative lens position.
[a] Independent *t*-test.
[b] χ^2test.
[c] Mann-Whitney test.

logistic regression analyses were conducted to determine the risk factors associated with the presence of zonulopathy. Variables with P values less than 0.05 in the univariate analysis were then added to the multivariate analysis. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used as an index to assess the performance of parameters in detecting the presence of zonulopathy.

3. Results

A total of 640 patients (248 male and 392 female) with age-related cataract aged 46.0–97.0 with a median of 70.0 years old were included. Zonulopathy was diagnosed based on intraoperative signs in 70 patients (10.9%). The demographic data and ocular biometric measurements are presented in Table 1. Compared with patients without zonulopathy, patients with zonulopathy were found to be older ($P < 0.001$), had shallower central ACD ($P < 0.001$), thicker lens ($P < 0.001$), shorter AL ($P = 0.010$), larger ALP ($P < 0.001$) and RLP ($P = 0.015$). No statistically significant difference was observed in gender, presenting visual acuity (PVA), or IOP between patients with or without zonulopathy ($P > 0.05$).

Table 2 and Fig. 2 present age-specific and gender-specific proportions of zonulopathy. The proportion of zonulopathy increased from 5.1% in the youngest age group of 45–60 years, to 8.9% and 8.2% in the age groups of 61–70 years and 71–80 years, respectively, and to 27.2% in the age group of >80 years ($\chi 2$ test of trend $P < 0.001$). Specifically, the proportion of zonulopathy was significantly higher in patients older than 80 years compared to patients in the younger age groups ($P < 0.001$). There was no significant difference in the proportion of zonulopathy among the three younger age groups ($P > 0.05$). And no significant differences existed in the proportions of zonulopathy between men and women in total and in different age groups ($P > 0.05$). Moreover, in men, the proportion of zonulopathy increased from 5.4% in the youngest age group of 45–60 years, to 7.2% and 6.3% in the age groups of 61–70 years and 71–80 years, respectively, and to 23.9% in the age group of >80 years ($\chi 2$ test of trend $P = 0.005$). And in women, the proportion of zonulopathy increased from 4.8% in the youngest age group of 45–60 years, to 9.9% and 9.1% in the age groups of 61–70 years and 71–80 years, respectively, and to 29.8% in the age group of >80 years ($\chi 2$ test of trend $P < 0.001$).

According to the univariate and multivariate logistic regression analyses, the risk predictors associated with the presence of zonulopathy in patients with age-related cataract were older age (OR = 1.042, $P = 0.035$) and shallower central ACD (OR = 0.834, $P < 0.001$) (Table 3). For every year increment in age, the risk of zonulopathy increased by 4.2%. For every 0.1 mm decrease in central ACD, the risk of zonulopathy increased by 16.6%.

ROC analysis was employed to assess the potential performance of age and central ACD as a combined determinant of zonulopathy in patients with age-related cataract (Fig. 3). The AUC was 0.747 (95% confidence interval [CI], 0.686–0.808), with a sensitivity of 55.9% (95% CI, 43.3%–67.9%) and a specificity of 84.2% (95% CI, 80.9%–87.1%).

4. Discussion

To the best of our knowledge, this is the first study reporting the prevalence of zonulopathy in age-related cataract, which was 10.9% in Chinese patients aged 45 years or older. The highest proportion of zonulopathy presented in the age-group of >80 years. Our findings suggest that patients with primary zonulopathy tended to be older, have shallower central ACD, thicker lens, shorter AL, larger ALP and RLP. Furthermore, older age and shallower central ACD were identified as risk predictors associated with the presence of zonulopathy in patients with age-related cataract.

The Cataract National Dataset of the UK summarized a total 55,567 cataract operations performed between 2001 and 2006 and zonular dialysis rate was identified to be 0.46% [8]. In another retrospective hospital-based study conducted at Queen Alexandra Hospital, medical records of 22,312 consecutive patients who underwent cataract surgery between 2004 and 2010 were reviewed. The study found that the incidence of preoperative or perioperative zonular dialysis was 0.50% [9]. A retrospective observational cohort study performed at Moorfields Eye Hospital reported an incidence rate of zonulopathy detected intraoperatively was 0.45% over a 5.5-year period from 2014 to 2019 [10]. However, these studies did not clarify the age distribution of the included patients or provide specific criteria for the diagnosis of zonulopathy.

The discrepancies in the proportions of zonulopathy between the prior data and our results may be attributed to several factors, including differences in age distributions, variations in inclusion and exclusion criteria, and different diagnosis criteria for zonulopathy. Zonulopathy can be associated to many pathologies including high axial myopia, pseudoexfoliation syndrome, Marfan's syndrome, homocystinuria, retinitis pigmentosa, Weil-Marchesani syndrome, microspherophakia, prior ocular trauma or prior ocular

Table 2
Age- and gender-specific ratios of zonulopathy in patients with age-related cataract.

Age (years)	Male			Female			Total		
	No. of Total Included Patients	No. of Cases with Zonulopathy	Ratio (%)	No. of Total Included Patients	No. of Cases with Zonulopathy	Ratio (%)	No. of Total Included Patients	No. of Cases with Zonulopathy	Ratio (%)
45–60	56	3	5.4	62	3	4.8	118	6	5.1
61–70	83	6	7.2	141	14	9.9	224	20	8.9
71–80	63	4	6.3	132	12	9.1	195	16	8.2
>80	46	11	23.9	57	17	29.8	103	28	27.2

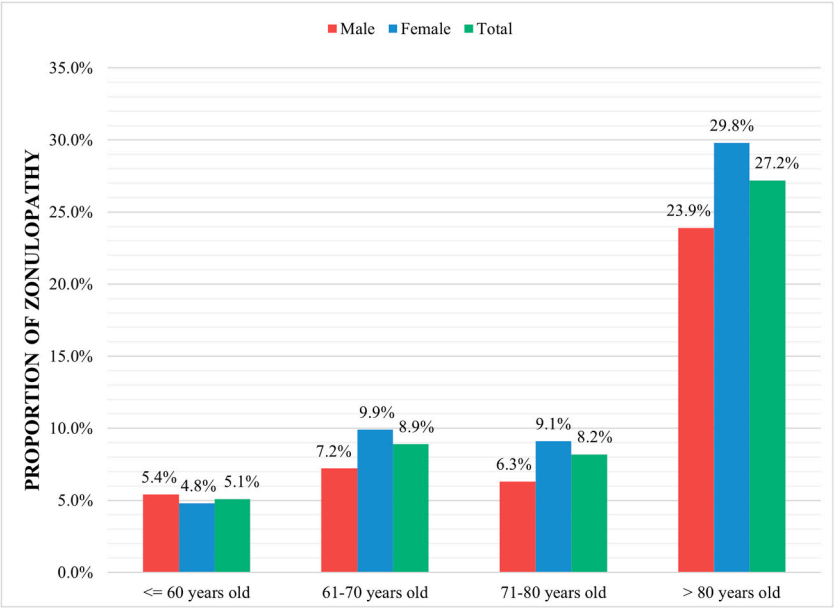

Fig. 2. Age-specific and gender-specific proportions of zonulopathy in patients with age-related cataract.

Table 3
Factors associated with zonulopathy in patients with age-related cataract.

Variable	Univariable		Multivariable			
	OR (95% CI)	*P* value	Estimated Regression Coefficient	OR (95% CI)	*P* value	VIF
Age	1.077 (1.046, 1.108)	<0.001	0.041	1.042 (1.003, 1.083)	0.035	1.249
Sex	1.241 (0.737, 2.090)	0.417				
Central ACD (0.1 mm)	0.821 (0.766, 0.880)	<0.001	−0.182	0.834 (0.765, 0.909)	<0.001	2.519
LT (0.1 mm)	1.139 (1.067, 1.217)	<0.001	–	–	–	2.226
AL (0.1 mm)	0.967 (0.941, 0.993)	0.013	–	–	–	1.342
ALP (mm)	0.141 (0.051, 0.393)	<0.001				
RLP (0.1 mm)	0.039 (0.003, 0.536)	0.015				

ACD, anterior chamber depth; LT, lens thickness; AL, axial length; ALP, absolute lens position; RLP, relative lens position; VIF, variance inflation factor.
ALP and RLP were not included in the multivariate logistic regression because of the multicollinearity with the AL and with each other.

surgery etc. [11–13] In our study, we specifically excluded patients who might have secondary zonulopathy. The result of this study was consistent with one of our previous studies, in which we employed the same inclusion and exclusion criteria. In that study, the incidence of primary zonulopathy was reported to be 6% in patients with age-related cataract [14].

Zonular strength is most effectively evaluated intraoperatively, particularly while manipulating the lens capsules [4]. The phenomena observed during the initiation and creation of CCC are considered the decisive signs for assessing zonular strength [5]. Therefore, in our study, wrinkling of lens anterior capsules with striae formation during CCC was used as the crucial criterion for the diagnosing zonulopathy.

In this study, older age was identified as one of the predictors for zonulopathy in patients with age-related cataract. Notably, the highest proportion of zonulopathy was found in patients aged older than 80 years. This observation aligns with the clinical experience of cataract surgeons, who have reported that the zonules tends to be more fragile with advanced age [15]. Assia et al. conducted a zonular stretch test on human donor eyes and demonstrated an age associated linear decrease in the distance of zonular fiber elasticity [16]. Furthermore, it has been found that the force required to rupture the zonules was reduced by approximately 30% in the zonular samples from donor eyes aged 85 years or older [17]. Besides that, ciliary muscle aging may also affect zonular strength. Sheppard et al. reported that the human ciliary muscle undergoes a general age-dependent antero-inwards shift throughout life, which may contribute to zonular laxity [18]. Moreover, LT increases with aging in adults [19]. In our study, we also found a similar age-related trend of increasing LT. Pearson correlation coefficient for LT and age were 0.443 ($P < 0.001$). Increased LT may worsen the burden of zonular fibers and result in increased incidence of zonulopathy in elderly patients.

In our study, we identified shallower central ACD as another predictor for zonulopathy in patients with age-related cataract. This result was consistent with the previous studies that reported similar findings in patients with conditions such as pseudoexfoliation syndrome, angle closure glaucoma and acute angle closure attack [14,20,21]. However, whether shallower central ACD is the cause or

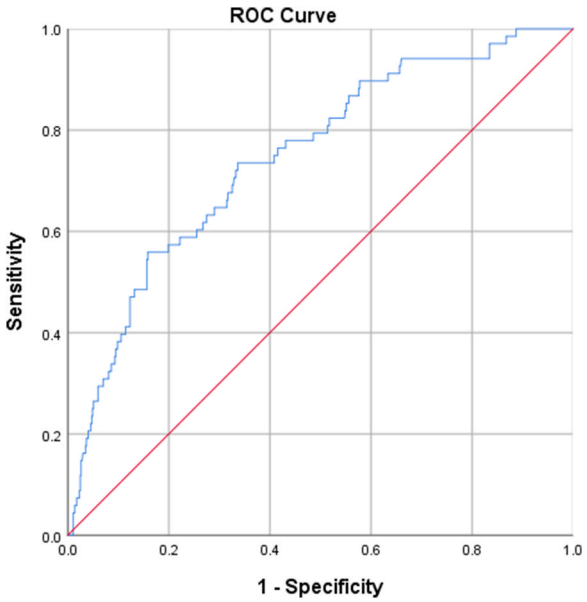

Fig. 3. ROC Curve of Logistic Regression Algorithm in Detecting Zonulopathy in Patients with Age-related Cataract using Combined Determinant of Age and Central ACD
ROC, receiver operating characteristics; ACD, anterior chamber depth.

the result of zonulopathy remains unclear. In our hypothesis, we propose that zonular weakness may lead to anterior movement of the lens diaphragm, resulting in a shallower central ACD.

Zonulopathy often leads to complex surgical course with intraoperative and postoperative complications. Awareness of the presence of zonulopathy through preoperative diagnosis can greatly improve surgical preparation, facilitate smoother operation, and enhance vision outcome. In our study, the combined determinant of age and central ACD achieved an AUC of 0.747 in diagnosing zonulopathy, which remains suboptimal for clinical application. Additional parameters such as ultrasound biomicroscopy, anterior segment optical coherence tomography, and other potential predictors should be evaluated for their roles in preoperative diagnosis of zonulopathy.

One strength of this study is the relatively large sample size, which helps minimize the bias and enhance the generalizability of the findings. Furthermore, to the best of our knowledge, this study represents the first investigation into the proportion of zonulopathy and related risk factors in Chinese patients with age-related cataract.

There are several limitations to consider in this study. Firstly, the diagnosis of zonulopathy was based on intraoperative signs, which is subjective. We mitigated this by having two senior ophthalmologists independently document the diagnosis and their consensus was used. Secondly, we did not specify the gonioscopic characters in the included patients, which might result in enrolling some primary angle closure suspect cases. It has been reported that patients with primary angle closure disease including PACS have higher proportion of zonulopathy compared to patients with age-related cataract only.[14] Therefore, the proportion of zonulopathy in our study may be slightly overestimated. Thirdly, the ethnic homogeneity of our study population (Chinese) may limit the generalizability of the results to other ethnic patient populations.

5. Conclusions

In conclusion, our present study demonstrated that primary zonulopathy is not uncommon among age-related cataract patients, particularly among patients over 80 years old. It is important for clinicians to be mindful of the potential presence of zonulopathy when performing cataract surgery in this patient population. Older age and shallower ACD were identified as the dependent risk factors for zonulopathy in these patients. Hence, for patients with age-related cataract who also have shallower ACD, relatively early cataract surgery (for example, before the age of 80 years old) should be advocated. And further research is desired to identify additional parameters that can enhance the sensitivity and specificity of preoperative diagnosis of zonulopathy.

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Patient consent for publication

Written informed consent was obtained from all the participants.

Data availability statement

The authors declare that all data supporting the findings of this study are available within the paper. The clinical data and images used in the study were collected at Beijing Tongren Hospital. They are not publicly available and restrictions apply to their use. All requests would require evaluation on an individual basis and can be made by contacting drqiaochunyan@sina.com and also with permission of Beijing Tongren Hospital.

Ethics declarations

This study was reviewed and approved by the Ethics Committee of the Beijing Tongren Hospital, with the approval number: TREC2022-KY003. All participants provided informed consent to participate in the study.

CRediT authorship contribution statement

Ye Zhang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hui Zhang:** Project administration, Investigation, Conceptualization. **Xudong Song:** Project administration, Conceptualization. **Mugen Liu:** Writing – review & editing. **Ningli Wang:** Supervision, Conceptualization. **Chunyan Qiao:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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