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ORIGINAL RESEARCH

The Role of the Vitreous Zonule in Preoperative Diagnosis of Zonular Laxity in Primary Angle-Closure Disease

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Purpose: This study aimed to evaluate the diagnostic value of the number of visible vitreous zonule (VZ) quadrants in predicting zonular laxity in patients with primary angle-closure disease (PACD).

Patients and Methods: This prospective cohort study collected data between the period of November 2021 and February 2024. PACD patients were enrolled, with one eye selected randomly for analysis. The main outcome was the association between the presence/number of quadrants with visible VZ and the presence of zonular laxity. The diagnostic capability of the number of quadrants with VZ in determining zonular laxity was evaluated.

Results: A total of 50 patients were enrolled in the study. Compared with the VZ group, the no VZ group was more likely to manifest zonula laxity (14 of 14 [100%] vs 19 of 36 [53%], P = 0.002). The zonular laxity group had fewer quadrants with visible VZ (1.18 ± 0.22 vs 2.93 ± 0.22, P < 0.001) than the normal group. The number of quadrants for zonular laxity detection achieved an area under the curve of 0.855 (P < 0.001). The highest Youden Index was observed when the number of quadrants was less than 3, indicating superior diagnostic capability for zonular laxity, with a sensitivity of 84.9% and specificity of 70.6%. The highest sensitivity (93.9%) was achieved when the number of quadrants was less than 4.

Conclusion: The study found a link between VZ lack and zonular laxity in PACD, enhancing diagnosis with fewer VZ quadrants, and highlighted VZ's diagnostic value.

Keywords: vitreous zonule, zonular laxity, primary angle-closure disease, diagnostic capability

Introduction

Primary angle-closure disease (PACD) is characterized by the occlusion of the anterior chamber angle, which may or may not be associated with elevated intraocular pressure and glaucomatous optic neuropathy.[1] This occlusion can occur due to various mechanisms, excluding other recognizable causes. The closure of the anterior angle can be attributed to two primary mechanisms: pupillary block and non-pupillary block.[2] It is noteworthy that multiple mechanisms frequently coexist in most patients, yet the relationship between these mechanisms remains inadequately understood.

Previous studies have demonstrated that the vitreous zonule (VZ) is an anatomical structure that has been identified by ultrasound biomicroscopy (UBM).[3–6] One study observed that primary angle-closure glaucoma (PACG) have fewer quadrants with visible VZ compared to primary angle-closure (PAC), and eyes with VZ deficiency tend to have narrower anterior chambers.[6] VZ is characterized as the zonular fibers that join the ciliary processes to the vitreous membrane in the ora serrata region, the anterior portion of which splits into a fork inserted into the zonular plexus.[7] Previous studies have found that VZ affects lens movement and thickness alterations. For instance, VZ can serve as a semi-rigid "pillar" behind the lens equator, offering direct resistance to the forward movement of the lens,[8] or the ciliary body has been

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shown to thicken and rotate anteriorly more following cleavage of the VZ with α-chymotrypsin.[7] These findings prompt speculation regarding the potential involvement of VZ in the pathogenesis of PACD as a structure that stabilizes the lens.

Zonular laxity has a high prevalence in PACD[9,10] and is linked to a variety of intraoperative complications and postoperative outcomes, including capsular rupture or constriction and eccentricity of the intraocular lens (IOL), which are essential factors in postoperative glaucoma recurrence.[10] Therefore, early detection of zonular laxity can aid in preparation for surgical challenges. While phacodonesis and asymmetry in anterior chamber depth (ACD) are two potential preoperative indicators,[11] these are not easy to detect in cases of occult zonular laxity.[12,13] Currently, there are no methods available for directly detecting zonular laxity prior to surgery. Although an indirect approach involves inferring zonular laxity by the observation of unequal distances from the ciliary process to the equator of the lens in different directions through UBM, this method remains unsuitable for a considerable portion of patients.[14]

The similarity between VZ and zonules, extending from origin to structure and function, has been extensively demonstrated.[8,15–18] However, existing research has not yet explored the possibility of using the number of quadrants with visible VZ as an indicator of zonular laxity. In this study, we aim-ed to address this knowledge gap by analyzing the relationship between the number of quadrants with visible VZ, as observed through UBM, and zonular laxity confirmed during surgery. Our innovative approach could potentially lead to the development of a novel preoperative method for predicting zonular laxity.

Material and Methods

Subjects

This study was a prospective, observational analysis of Chinese patients with PACD. The study received approval from the ethics committee of Peking University People's Hospital (Grant number: 2022PHB256-001) and adhered to the principles of the Declaration of Helsinki. Approval from the Institutional Review Board was also obtained. All subjects provided written informed consent. The recruitment of PACD patients took place at the glaucoma clinic of Peking University People's Hospital from November 2021 to February 2024.

Patients diagnosed with PACD were recruited, with either the left or right eye of each patient randomly selected for inclusion. If both eyes of a patient met the inclusion criteria, one eye was selected randomly using a computer-generated random number list in SPSS (version 26.0, Inc., Chicago, Illinois, USA) assigning 1 = right eye, 2 = left eye) to avoid inter-eye correlation bias. According to the classification system of the International Society of Geography and Epidemiology of Ophthalmology (ISGEO), all eyes were categorized as primary angle-closure suspect (PACS), PAC, or PACG. PACS was diagnosed when an eye showing the peripheral iris contacted with the trabecular meshwork at the posterior part of the anterior chamber angle but without elevated IOP or peripheral anterior synechia (PAS). A PACS eye with elevated IOP over 21 mmHg or exhibiting PAS, yet lacking optic nerve damage, was defined as PAC; PACG eyes occurred optic nerve damage based on PAC.[19] PACD patients were eligible for inclusion if they met the following criteria: a confirmed diagnosis of primary angle-closure disease (PACS, PAC, or PACG) according to ISGEO definitions; availability of high-quality preoperative UBM images suitable for VZ assessment; underwent phacoemulsification cataract surgery or clear lens extraction that allowed intraoperative evaluation of zonular condition; and both preoperative and intraoperative signs of zonular laxity and loss were used to identify and classify patients, as described in detail below ("Assessment of the status of zonules" section). Exclusion criteria included a history of ocular conditions potentially leading to secondary angle closure, use of medications that could affect anterior chamber configuration, diagnostic uncertainty based on history, symptoms, or examination findings, inability to undergo gonioscopy or UBM examination, and UBM images of inadequate quality for reliable analysis. Because no prior data were available to estimate effect size for the diagnostic performance of visible VZ quadrants, a formal power calculation was not feasible. The sample size of 50 eyes was determined by the availability of consecutive PACD cases meeting inclusion criteria with high-quality UBM images suitable for quantitative analysis.

Ophthalmologic Examinations

All participants underwent an extensive eye examination. This included a measurement of the best corrected visual acuity (BCVA), an IOP assessment using Goldmann applanation tonometry (manufactured by Haag-Streit, Koniz, Switzerland),

a thorough slit-lamp biomicroscopy, and a stereoscopic assessment of the optic disc with a 90-diopter lens (produced by Volk Optical, Inc., Mentor, OH, USA).

A glaucoma specialist (H.J.W.) performed gonioscopy in a dimly lit room using a Zeiss-style four-mirror gonioscopy lens (Model G-4; Volk Optical, Inc.) at a magnification of ×16, both with and without indentation. The aim was to calculate the average gonioscopic angle width (determined by adding the Shaffer grade in each of the four quadrants and dividing by four) and to check for PAS.

Axial length (AXL) was determined using five measurements taken with the IOLMaster, with the average value used for analysis. Optical coherence tomography (Spectralis HRA+OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) was employed to detect any defects in the retinal nerve fiber layer. Additionally, a visual field test was also carried out using the Humphrey Field Analyser (Carl Zeiss Meditec, Inc., Dublin, CA, USA) to identify any characteristic defects in the glaucomatous visual field.

Ultrasound Biomicroscopy

Simultaneously, trained operators performed UBM (Aviso, Quantel Medical, Inc., Bozeman, MT) using a 50MHz transducer. All patients were imaged in a well-lit room while positioned supine. Measurements were captured from the superior, inferior, temporal, and nasal quadrants of both eyes. If images of VZ were displayed on the monitor during dynamic scanning, they were frozen and saved. Certain zonules connecting directly to the posterior lens equator, referred to as the posterior VZ insertion zone and posterior lens equator (PVZ INS-LE),[7,8,18] were also categorized and included as part of VZ (Figure 1).

If clear evidence of VZ was detected in at least one quadrant (temporal, nasal, superior, or inferior) in the UBM images, the patient was assigned to the vitreous zonule group (VZG). The number of quadrants with visible VZ and their corresponding locations were recorded for each patient. Eyes where UBM images from all four quadrants showed no evidence of VZ were classified as the no vitreous zonule group (NVZG). Images of poor quality or those with inadequate information, such as those in which the ciliary process could not be fully visualized to determine the presence of VZ, were excluded from the analysis.

Assessment of the Status of Zonules

Following the administration of local anesthesia and the establishment of sterile conditions, a temporal corneal incision was made. Standard phacoemulsification cataract surgery was then performed, and a foldable intraocular lens was inserted into the capsular bag. Ultimately, the viscoelastic was exchanged with balanced salt solution. The incision was then hydrated to ensure that it was water-tight. In cases where there was extensive PAS, goniosynechialysis was performed prior to phacoemulsification. This procedure involved using a blunt cyclodialysis spatula to press against the peripheral edges of the iris near the area where the angle was adhered.

Preoperative and intraoperative indicators were employed to evaluate zonular laxity, and surgical videos were captured for subsequent analysis. Preoperative signs suggestive of zonular weakness included iridodonesis, phacodonesis, asymmetry or shallowness of ACD between eyes, pigmentation at the anterior chamber angle, rounding of the lens equator, decentration of the fetal nucleus, anisometropia, and abnormal zonular fiber configuration or anterior lens displacement observed on UBM or anterior segment-optical coherence tomography. These features indicated potential zonular laxity prior to surgery. Intraoperative zonular laxity was inferred from dynamic signs observed during phacoemulsification, including (1) radial folds on the anterior capsule during continuous circular capsulorhexis (Figure 2); (2) central shift of the equatorial portion of the capsular bag during ultrasound phacoemulsification; (3) unusual movement of the anterior capsular opening and posterior capsular bag during cortical irrigation and aspiration; (4) change in the shape of the anterior capsular opening from its initial circular form after capsulorhexis, becoming irregularly elliptical or decentered; (5) capsular wrinkling with striae formation extending to the periphery; (6) posterior capsule laxity or infolding during cortex removal; (7) loss of zonular fibers with visible peripheral capsule; and (8) persistent decentration of the intraocular lens.[11,20,21] Patients were classified into the zonular laxity group if they exhibited one or more of the previously mentioned signs. If not, they were categorized as the normal group.

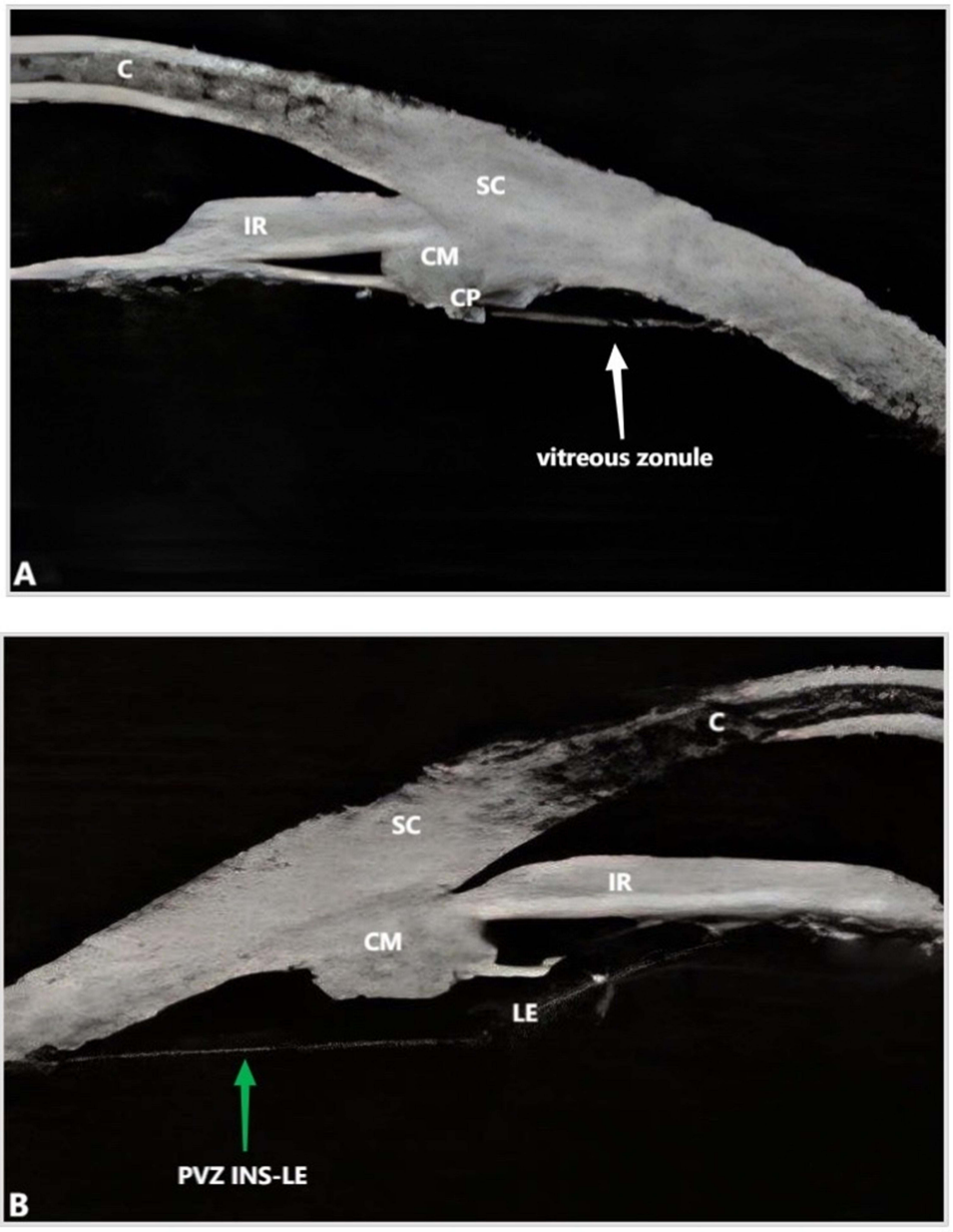

Figure 1 Ultrasound biomicroscopy (UBM) images showing vitreous zonule (VZ) and posterior VZ insertion zone and posterior lens equator (PVZ INS-LE). UBM images of a 67-year-old male patient. (**A**) The white arrow indicates the VZ. (**B**) The green arrow indicates the PVZ INS-LE.

Statistical Analysis

Statistical analysis was performed using SPSS. Descriptive statistics were computed for continuous data, such as means and standard deviations. Grouping was based on whether the number of visible VZ quadrants on the UBM image was less than 2, 3, or 4. The Mann–Whitney *U*-test was utilized to compare the number of quadrants between the zonular laxity and normal groups. The chi-square test was employed to analyze the variations with regard to the presence of VZ and the number of quadrants less than 2, 3, and 4 between the zonular laxity and normal groups. Correlation analysis was conducted to investigate the relationship between zonular laxity and the presence of VZ as well as the number of quadrants. The Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) were computed for the number of quadrants. In order to evaluate the diagnostic capability of the number of visible VZ quadrants for zonular laxity, the following metrics were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) for the various groups of VZ quadrant

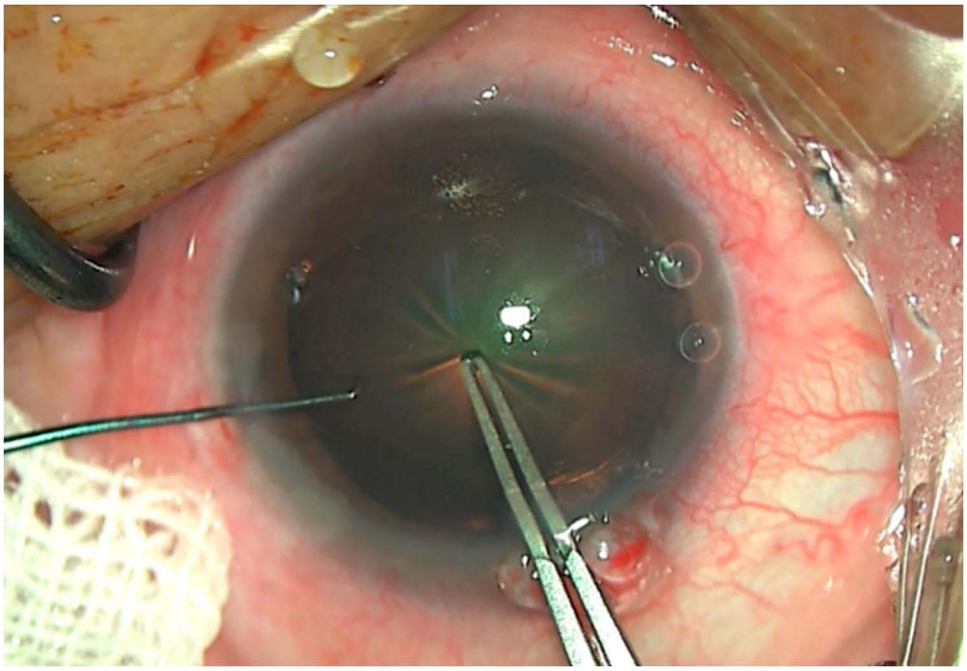

Figure 2 Radial folds of the anterior lens capsule during continuous circular capsulorhexis. Radial folds are observed on the anterior lens capsule surface during the creation of continuous circular capsulorhexis, reflecting the presence of zonular laxity.

numbers (less than 2, 3, and 4). The likelihood ratio is used to assist in assessing diagnostic capability. A large positive likelihood ratio helps to confirm the diagnosis while a small negative likelihood ratio aids in exclusion.[22] In this study, positive likelihood ratios > 10 and negative likelihood ratios < 0.1 were used to assess superior diagnostic value. To ensure reliability in measurements, inter-observer consistency was assessed using Kappa statistics for categorical variables ("Presence of VZ" and " Presence of zonular laxity") and Intraclass coefficient (ICC) for the continuous variable ("Number of quadrants with VZ"). Kappa values > 0.75 indicated excellent agreement, and ICC values > 0.9 denoted excellent reliability. A p-value less than 0.05 was considered statistically significant and the hypothesis tests were all two-sided. Data analysis was conducted from August 2023 to February 2024.

Results

Table 1 shows all demographic characteristics and ocular parameters for 50 eyes of 50 patients, including 13 cases of PACS, 14 of PAC, and 23 of PACG. The mean (SD) age of the cohort was 69.1 (9.6) years, with a gender distribution of 20 males (40%) and 30 females (60%). No significant differences in gender, age, BCVA, AXL, baseline IOP, status of the zonules, and the presence and number of quadrants with VZ were observed among the three groups.

Table 2 illustrates the relationship between zonular laxity and VZ. A significant disparity was observed in the number of VZ quadrants between the zonular laxity and normal groups (1.18 ± 0.218 vs 2.93 ± 0.220, $P < 0.001$). Moreover, a notable association (r = - 0.448) was discovered between the presence of VZ and zonular laxity. The presence of zonular laxity showed a significant difference between VZG and NVZG (19 of 36 [53%] vs 14 of 14 [100%], $P = 0.002$). Table 3 categorized the groups according to the number of VZ quadrants and analysed the association between zonular laxity and the number of VZ quadrants in each group. The presence or absence of zonular laxity was found to be significantly associated with VZ quadrants less than 2, 3, and 4 ($P < 0.001$, < 0.001, =0.02, respectively). Based on these results, individuals with zonular laxity tended to manifest a lower incidence of VZ presence and fewer visible VZ quadrants. The ROC curve for zonular laxity diagnosis using the number of quadrants with VZ is shown in Figure 3. An AUC value of 0.855 (95% CI, 0.751–0.958; $P < 0.001$) was obtained, indicating a moderate diagnostic capability of the number of quadrants for zonular laxity detection. The highest Youden index (sensitivity + specificity - 1) was observed at a cutoff value of 2.5. Subgroup analysis according to axial length demonstrated consistent diagnostic performance of the

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Table 1 Demographic, Ocular Characteristics, VZ Parameters of Eyes with PACD

Characteristic and Parameter	PACS (N=13)	PAC (N=14)	PACG (N=23)	*P* value
Sex, No. (%)				
Female	10 (77)	10 (71)	10 (44)	0.09
Male	3 (23)	4 (29)	13 (56)	
Age, mean (SD), y	70.8 (4.0)	66.4 (1.8)	69.8 (1.6)	0.46
BCVA, mean (SD), decimal	0.36 (0.05)	0.44 (0.07)	0.39 (0.06)	0.66
AL, mean (SD), mm	22.99 (0.24)	21.98 (0.34)	23.13 (0.33)	0.06
Baseline IOP, mean (SD), mm Hg	17.10 (0.89)	18.45 (2.75)	17.30 (0.87)	0.87
Presence of VZ, No. (%)				
With	10 (77)	10 (71)	16 (70)	0.89
Without	3 (23)	4 (29)	7 (30)	
Number of quadrants with visible VZ, mean (SD)	1.92 (0.40)	1.71 (0.38)	1.74 (0.30)	0.77
Presence of zonular laxity, No. (%)				
With	9 (69)	9 (64)	15 (65)	0.96
Without	4 (31)	5 (36)	8 (35)	

Abbreviations: BCVA, best corrected visual acuity; AL, axial length; IOP, intraocular pressure; VZ, vitreous zonule; PACS, primary angle-closure suspect; PAC, primary angle-closure; PACG, primary angle-closure glaucoma.

Table 2 The Presence and the Number of Visible VZ Quadrants Between Groups with and without the Zonular Laxity

Variables	Zonular Laxity	Without Zonular Laxity	r	*P* value
Number of quadrants of visible VZ	1.18 (0.218)	2.94 (0.220)	− 0.594	< 0.001*
Presence of VZ, No. (%)				
VZG	19 (53)	17 (47)	− 0.448	0.002**
NVZG	14 (100)	0 (0)		

Notes: *The Mann–Whitney *U*-test. **The chi-square test.
Abbreviations: VZ, vitreous zonule; VZG, vitreous group; NVZG, no vitreous group.

Table 3 The Association Between Zonular Laxity and The Number of Visible VZ Quadrants with Different Grouping Criterion

Criterion	Zonular Laxity	Without Zonular Laxity	*P* value
Number of visible VZ quadrants ≥ 2 or < 2, No. (%)			
≥ 2	13 (45)	16 (55)	< 0.001*
< 2	20 (95)	1 (5)	
Number of visible VZ quadrants ≥ 3 or < 3, No. (%)			
≥ 3	5 (29)	12 (71)	< 0.001*
< 3	28 (85)	5 (15)	
Number of visible VZ quadrants = 4 or <4, No. (%)			
= 4	2 (29)	5 (71)	0.02*
< 4	31 (72)	12 (28)	

Note: *The chi-square test.
Abbreviation: VZ, vitreous zonule.

number of visible VZ quadrants in predicting zonular laxity. The AUC was 0.826 (95% CI, 0.688–0.964) with the highest Youden index of 2.5 for eyes with AL ≤ 22.5 mm, and 0.906 (95% CI, 0.753–1.000) with the highest Youden index of 1.5 for eyes with AL > 23.5 mm ($P < 0.05$ for both), indicating stable diagnostic accuracy across subgroups (Supplementary Figure 1).

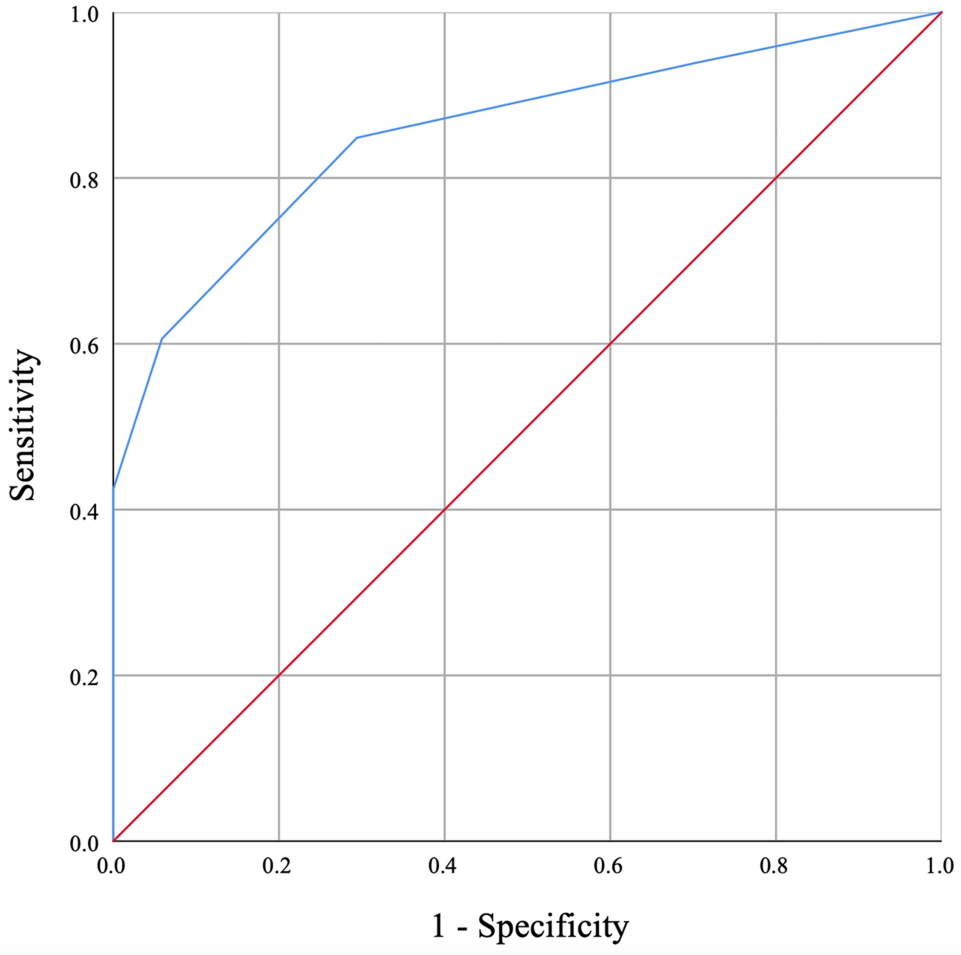

Figure 3 Receiver Operating Characteristic (ROC) curve for diagnosing zonular laxity using the number of visible vitreous zonule (VZ) quadrants. The red line represents the ROC curve based on the number of visible VZ quadrants for diagnosing zonular laxity, while the blue diagonal line indicates the reference line of no discrimination (Area under the curve (AUC) = 0.5). The overall AUC was 0.855 ($P < 0.001$), indicating strong diagnostic performance of the number of visible VZ quadrants in predicting zonular laxity in patients with primary angle-closure disease. Subgroup ROC analyses by axial length are provided in Supplementary Figure 1.

Table 4 provides the sensitivity, specificity, PPV, NPV, PLR, and NLR for different cutoff values, based on three grouping criteria for the number of quadrants. Optimal sensitivity (93.9%) and NPV (72.4%) were achieved when the number of VZ quadrants was less than 4. Optimal specificity (94.1%) and PPV (95.2%) were achieved when the number of VZ quadrants was less than 2, with a PLR greater than 10 under this criterion. However, none of the criteria had both a PLR greater than 10 and an NLR less than 0.1. Consequently, in the current study, considering the highest Youden index, the number of quadrants with visible VZ less than 3 provided a superior comprehensive diagnostic accuracy for zonular laxity. At this threshold, the sensitivity was 84.9%, and the specificity was 70.6%.

Table 4 Performance of the Number of Quadrants with VZ for Diagnosing Zonular Laxity

Criterion	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	PLR (95% CI)	NLR (95% CI)
Number of quadrants with VZ						
< 2	60.6 (47.1–74.1)	94.1 (87.6–100.6)	95. 2(89.3–101.1)	55.2 (41.4–69.0)	10.30 (−16.30–36.87)	0.41 (0.28–0.56)
< 3	84.9 (74.9–94.8)	70.6 (58.0–83.2)	84.9 (74.9–94.8)	70.6 (58.0–83.2)	2.88 (1.38–4.39)	0.21 (0.10–0.33)
< 4	93.9 (87.3–101.0)	29.4 (16.8–42.0)	72.1 (60.0–84.5)	72.4 (58.9–84.0)	1.33 (1.21–1.45)	0.21 (0.09–0.32)

Abbreviations: VZ, vitreous zonule; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

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Table 5 Consistency Analysis Results

Parameters	Kappa/Intraclass Coefficients	
	Intra-Observer	Inter-Observer
Presence of VZ*	0.83	0.85
Number of quadrants with visible VZ**	0.93	0.91
Presence of zonular laxity*	0.81	0.80

Notes: *Kappa statistics. **Intraclass coefficient.
Abbreviation: VZ, vitreous zonule.

The intraobserver Kappa for "Presence of VZ" and "Zonular laxity" were 0.83 and 0.81, showing substantial agreement. Interobserver Kappa for these were 0.85 and 0.80, indicating similar substantial agreement. The ICC for "Number of quadrants with VZ" was 0.93 intraobserver and 0.91 interobserver, demonstrating excellent consistency. These findings affirm the reliability and repeatability of the key measurements in this study (Table 5).

Discussion

The relationship between VZ and other intraocular anatomical structures in PACD has been previously described in several studies,[5–8,18] but the intrinsic role of VZ in pathogenesis remains elusive. Lens stability abnormalities, recognized as one of the mechanisms of PACD pathogenesis, have reached a consensus.[1,23–25] Nonetheless, the current preoperative diagnostic method of zonular laxity in PACD was not satisfied. Therefore, this study investigated the presence and number of quadrants with visible VZ in zonular laxity and normal groups, revealing that patients with absent or reduced VZ were more likely to have zonular laxity. Further classification of patients by the count of VZ demonstrated a disparity in zonular laxity cases across the groups, regardless of whether the number of quadrants was less than 2, 3, or 4, serving as a threshold. This suggests the potential of the number of quadrants with visible VZ as a discriminator between the zonular laxity and normal groups. To the best of our knowledge, this is the first study to correlate VZ deficiency with zonular laxity, providing novel insights for subsequent research into the role of VZ in PACD pathogenesis.

In phacoemulsification combined with anti-glaucoma surgery, zonular laxity is associated with a variety of intraoperative and postoperative complications, including intraoperative vitreous prolapse, capsular rupture or constriction, retention of lens material, and postoperative complications such as anterior capsule contraction, pseudophakodonesis, and decentration/dislocation of the IOL.[10,21,26] Early detection of zonular laxity can facilitate the surgeon to implement a series of measures, such as intraoperative use of a capsular tension ring or sutured/ scleral fixated capsular tension segments,[20] to minimize the associated complications. However, preoperative detection of zonular laxity presents a challenge due to the difficulty in directly visualizing the zonules, with most cases manifesting as occult zonular laxity.[12] At present, preoperative diagnosis is mainly based on indirect signs and ocular biometric characteristics observed by UBM and slit-lamp examination. These may include a shallower ACD, uneven ACD among the quadrants, a large binocular ACD discrepancy, phacodonesis, lens shaking, anterior displacement of iris lens diaphragm, and unequal distances from the ciliary process to the equatorial portion of the lens in different directions.[14,27] Chen et al also identified binocular LV differences as a valid discriminator of zonular laxity.[28] Nevertheless, these diagnostic methods are suboptimal. In a previous study, preoperative findings from combined UBM and slit-lamp microscopy based on some of the above diagnostic indicators to determine zonular disorders were overlooked in approximately 70% of cases, with a sensitivity of only 29.2%.[12] Furthermore, despite the high AUC value of 0.972[29] for the diagnosis of binocular ACD discrepancy, in this study ACD discrepancy was combined with other parameters to achieve high diagnostic accuracy and were limited to patients with monocular involvement. Additionally, not all cases of zonular laxity will exhibit the physical indications described above, and full dilation of pupil by slit-lamp examination may exacerbate pupillary block and there is a risk of increased IOP elevation in patients with PACD.[30] Given that the majority of PACD is binocular diseases,[31] the large ACD and LV discrepancy may not be sufficiently prominent due to similar anatomical characteristics in both eyes.[28] Moreover, it is not easy to compare unequal distances between the ciliary

process and lens equator through UBM if there is uniform zonular laxity in all directions.[14] There is an urgent need for the development of innovative preoperative diagnostic techniques that offer superior accuracy.

We evaluated the capability of calculating the number of quadrants with visible VZ by UBM for diagnosing zonular laxity. The AUC value was 0.855, indicating a moderate diagnostic capability. When the criterion was set at less than 3 VZ quadrants, the comprehensive diagnostic capability for zonular laxity was high, although other statistical indicators were unable to show a favorable result. To detect more patients for zonular laxity, more sensitive diagnostic criteria were required. Employing a threshold of less than 4 VZ quadrants minimized the risk of overlooking zonular laxity while maximizing the probability of identifying normal zonules, thus evidencing a sensitive diagnostic capability. Although the specificity is poor at this point, it is possible that the inherent nature of the UBM may lead to an underestimation of VZ quantity. In addition, considering that PLR greater than 10 is a strong positive test result and NLR less than 0.1 is a strong negative predictor,[22] when the criterion is less than 4, NLR is closer to 0.1, indicating a relatively reliable negative predictive outcome.

As for glaucoma, Shon et al demonstrated a higher percentage of PACG in patients without VZ,[6] and our previous study found a progressive decrease in VZ quantity from healthy eyes to PACS, PAC, and PACG.[5] Both studies described narrower anterior chamber characteristics, a more anterior rotation of ciliary body and a greater LV in patients without VZ, suggesting that VZ deficiency could potentially contribute to the development of PACD. Nevertheless, the interplay between VZ and various ocular anatomical structures in PACD patients remains poorly understood. An experimental study observed decreased anterior rotation of ciliary body with age and increased anterior chamber angle narrowing after α-chymotrypsin-induced lysis in rhesus monkeys.[7] Another experiment demonstrated a synergistic forward motion of the ciliary body and VZ in the human eye.[18] These findings lead to the proposition that VZ might play a role in restricting the anterior movement of the ciliary body. In addition, the PVZ-INS LE, which connects the lens equator to the posterior VZ insertion zone, functions as a "semi-rigid pillar", limiting excessive anterior movement of the lens.[8,17,18] According to these observations, there is a close relationship between VZ and the ciliary body and lens, which are affected by the condition of the zonules. This is consistent with the findings of our current study, which showed that PACD eyes with VZ deficiency exert lower backward pull force on the ciliary body and lens, causing them to shift forward and increase the likelihood of zonular laxity. However, the reverse mechanism may also occur. A chronically shallow anterior chamber and anterior rotation of the ciliary body could impose continuous mechanical traction on the VZ fibers, leading to their gradual stretching or rupture. This reciprocal relationship warrants further verification in future longitudinal imaging studies. It is also noteworthy that VZ and the zonules share similar embryonic origins and structural characteristics. Both are secreted by ciliary epithelial cells and originated from mesodermal tissue, forming in the fourth month of fetal life, and are also known as tertiary vitreous.[15,16] It is possible that the VZ may be similarly altered in eyes with zonular disorders due to their shared origin. As such, the deficiency of VZ may be one of the mechanisms underlying zonular laxity in PACD.

Although this study has enhanced our understanding of the role of the VZ in the pathogenesis of PACD and proposed a valuable method for preoperative prediction of zonular laxity, several limitations should be acknowledged. Firstly, the relatively small sample size and the single-center design may introduce selection bias and limit the generalizability of the findings to broader PACD populations, as patients were selectively enrolled from a tertiary referral center with high-quality UBM images. Nevertheless, the significant results and excellent inter-observer reliability support the robustness of the data. Secondly, due to the inherent limitation of UBM imaging, it is not possible to confirm whether the invisibility of the VZ truly represents absence rather than insufficient visualization. Future multicenter studies with larger and more diverse populations, as well as advanced imaging techniques, are warranted to further validate and refine these findings.

In this prospective, observational study, patients with an absence or reduction of VZ are more likely to exhibit zonular laxity. Counting VZ using UBM emerges as a superior method for diagnosing zonular laxity. Our results indicate that when the criterion is set at a number of VZ quadrants less than 3, it achieves a high comprehensive diagnosis capability for zonular laxity while selecting the number of VZ quadrants less than 4 yields high sensitivity with a low rate of ignored diagnosis. This assists us in minimizing the complications associated with zonular laxity through adequate preoperative and intraoperative preparation and intervention. By providing surgeons with insights into the status of the zonules before the surgery, this method could enhance surgical planning and preparation, ultimately contributing to better

patient outcomes. The connection between VZ and the zonules is strong, both structurally and functionally, suggesting it may play a potential role in the pathogenesis of PACD. Future studies are warranted to further investigate the role and clinical significance of VZ.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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