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学位論文

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（超音波生体顕微鏡を用いた原発閉塞隅角病の毛様小帯脆弱の評価）

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Evaluation of weakness of ciliary zonule in primary angle closure diseases using ultrasound biomicroscopy

Short Title: Zonular weakness in UBM

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Running Title: Zonular weakness in UBM

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Abstract

Purpose: To evaluate zonular weakness before cataract surgery in eyes with primary angle closure disease (PACD). **Study design:** Retrospective **Methods:** This study was conducted at the University of the Ryukyus, Okinawa, Japan. We analyzed data from 133 eyes in 106 consecutive patients with PACD who underwent cataract surgery. PACD included PACS (primary angle closure suspect), PAC (primary angle closure), and PACG (primary angle closure glaucoma). We compared 68 eyes with zonular weakness and 65 eyes without zonular weakness, as identified during surgery. We developed three new ultrasound biomicroscopy (UBM) parameters. The SS-CP and SS-LS parameters were defined as the vertical distance between the scleral spur (SS) and the ciliary process (CP) or the lens surface (LS), respectively. The CP-LS parameter was defined as the distance between the CP and the LS. **Results:** Of the 133 eyes, 18 (13.5%), 50 (37.6%), and 65 (48.9%) were diagnosed with PACS, PAC, and PACG, respectively. Of the 68 eyes with zonular weakness, 8 eyes needed sulcus fixation of the intra ocular lens (IOL) because of lens subluxation. CP-LS was longer in eyes that required sulcus fixation of the IOL than in those that did not require sulcus fixation of the IOL ($P < 0.01$).
Conclusions: A longer distance between the CP and the edge of the lens surface (CP-LS) necessitated a more difficult cataract surgery and greater frequency of sulcus fixation of the IOL. UBM examination is useful for detecting zonular weakness before surgery in PACD eyes.
Keywords: zonular weakness, PACD, UBM, cataract surgery

INTRODUCTION

Glaucoma causes irreversible blindness and visual impairment and is the second leading cause of blindness worldwide, following cataracts [1]. Yih-Chung Tham et al. estimated that the number of glaucoma cases worldwide will reach 111.8 million in 2040, wherein approximately 80 million people will experience primary open-angle glaucoma (POAG), and the remaining 32 million people will experience primary angle closure glaucoma (PACG) [2]. The Kumejima Study reported prevalence rates of 2.0% and 4.0% for PACG and POAG, respectively; additionally, they reported a prevalence rate of 3.7% for bilateral blindness with PACG, which was 6 times higher than that for POAG (0.7%) [3, 4]. The average rates of blindness in Asian countries were 20.1% for PACG and 8.6% for POAG [5]. Thus, PACG tends to cause bilateral blindness more frequently than does POAG.

The Asian Pacific Glaucoma Society recommends laser treatment or trabecular surgery to correct the abnormal anatomy in glaucoma and reports that medical treatment is suitable in combination with laser peripheral iridotomy (LPI) or cataract extraction after LPI [5]. According to the Preferred Practice Pattern guidelines of the American Academy of Ophthalmology (AAO), LPI is the first-line treatment for primary angle closure disease (PACD), including acute primary angle closure (APAC); cataract surgery should be indicated after considering its risks and benefits [6]. In Japan, LPI or lens extraction is recommended as a first-line treatment for PAC (including PACG) in the guidelines for glaucoma [7]. LPI is useful for relative pupillary block [5] but is not adapted for plateau iris syndrome and lens-induced angle closure glaucoma (ACG) [8]. The effectiveness of phacoemulsification and aspiration with intraocular lens implantation (Phaco + IOL) for patients with PACD and coexisting cataracts has been demonstrated [9]. In previous studies, Phaco + IOL was more effective in lowering the intraocular pressure (IOP) and reducing the number of anti-glaucoma medicines than LPI [10]. Additionally, Phaco + IOL is more effective than LPI in patients with APAC [11, 12]. A recent randomized controlled trial reported that Phaco + IOL was more useful and cost-effective when compared with LPI in reducing the IOP [13]. However, it might be technically difficult to perform Phaco + IOL for patients with PACD because of the frequent coexistence of a shallow anterior chamber, a large bulky lens, iris atrophy secondary to ischemia, and associated zonular weakness [5]. The use of a capsular tension ring [14], iris hooks [15, 16], or capsular stabilization should be considered in cases where zonular weakness is detected pre- or intra-operatively [17]. Moreover, if the zonular weakness is severe, scleral suture fixation might prove more effective than in-the-bag IOL implantation [18].

Zonular weakness is sometimes observed in eyes with a history of trauma, intraocular surgery, pseudoexfoliation syndrome, high myopia, retinitis pigmentosa, uveitis, endophthalmitis, intraocular tumor, and genetic disease (e.g., spherophakia, Marfan syndrome, and Weill–Marchesani syndrome). Zonular weakness can be easily detected in patients with lens dislocation (phacodonesis) or deposition of pseudoexfoliation material in the pupil or anterior surface of the lens. However, cases of zonular weakness in the absence of these conditions have been reported; some studies described intraoperative findings that were indicative of zonular weakness, such as capsule wrinkling [19] or shifted distance of the lens capsule at the start of continuous curvilinear capsulorhexis [20, 21]. Recently, we reported a relatively high prevalence (5.4%; 10 eyes) of zonular weakness during cataract surgery in eyes with PACD (184 eyes) [22]. Hence, the preoperative diagnosis of zonular weakness in PACD eyes might be of importance.

The ultrasound biomicroscopy (UBM) findings of zonular abnormalities (e.g., stretching or missing) in association with pseudoexfoliation, spherophakia, surgical procedures, trauma, and Marfan syndrome have been reported [23, 24]. To the best of our knowledge, no study has investigated zonular weakness before cataract surgery. This study aimed to evaluate the presence of zonular weakness before cataract surgery in patients with PACD and coexisting cataracts using UBM.

PATIENTS and METHODS

This retrospective case–control study comprised 875 eyes with PACD that underwent Phaco + IOL between October 2015 and May 2017, after excluding cases with severe phacodonesis, lens subluxation, history of trauma, and pseudoexfoliation that were detected before surgery. A total of 68 consecutive eyes from 56 patients were identified with zonular weakness that was detected at the time of surgery. Intraoperative signs that indicate the presence of zonular weakness include capsule wrinkling during continuous curvilinear capsulorrhexis (CCC) [19] and/or infolding of the peripheral capsule during irrigation/aspiration of the cortex [21]. We identified the patients who presented with this sign intraoperative as having zonular weakness whereas those without this sign were categorized as without zonular weakness. All surgical procedures were performed by skilled surgeons and they routinely evaluated all patients for the presence of zonular weakness. The presence or absence of zonular weakness during surgery was stated in the medical record each time. Sixty-five consecutive eyes from 50 patients (evaluated between

March 2017 and May 2017) who were diagnosed as having no zonular weakness in the medical record intraoperative findings were used as controls. The grade of cataract was assessed using the Emery–Little classification.

PACD was diagnosed by static gonioscopy, before surgery, on the basis of the International Society Geographical and Epidemiological Ophthalmology classification with a <180° visibility of the scleral spur (SS) and one or more of the following: IOP exceeding 21 mmHg and presence of peripheral anterior synechiae (PAS) reaching the SS or beyond. Primary angle closure suspect (PACS) was diagnosed when the eye had an occludable angle but not PAC, i.e., without any IOP elevation and PAS. PACG was diagnosed as the presence of an occludable angle with glaucomatous optic neuropathy.

The Institutional Review Board of University of the Ryukyus reviewed and approved our retrospective study and waived the requirement of informed consent. The present study followed the tenets of the Declaration of Helsinki.

UBM parameters

UBM examination is used as the standard preoperative procedure for cases of PACD in our facility. The examinations were performed by skilled technicians before surgery at the 12 o'clock (superior), 3 or 9 o'clock (nasal or temporal), and 6 o'clock (inferior) positions of the eyes in a dark setting using a UD-1000 instrument (Tomey, Aichi, Japan) with a 40 MHz transducer probe.

The SS, the top of the ciliary process (CP), and the edge of the lens surface (LS) were identified using the UBM images (Fig. 1). The edge of the LS was defined as the endpoint that can be seen in the UBM image. The baseline was identified as a line passing through both the SS and a point on the trabecular meshwork 500 μm anterior to the SS. The SS-CP parameter was defined as the length of a perpendicular line drawn from the CP to the baseline. The SS-LS parameter was defined as the length of a perpendicular line drawn from the edge of the LS to the baseline. The CP-LS parameter was defined as the length between the CP and the LS. These three parameters (SS-CP, SS-LS, and CP-LS) were measured using the built-in caliper of the UBM machine, and the maximum values among the four quadrants were used for analysis.

Analysis

Sixty-eight eyes with zonular weakness were compared with 65 eyes without zonular weakness. Among the 68 eyes with zonular weakness, eight needed sulcus fixation of the IOL because of lens subluxation during surgery. Consequently, comparisons between eight eyes with sulcus fixation and 125 eyes without sulcus fixation of the IOL were made in this study. The parameters used to compare between eyes with and without zonular weakness or between eyes with and without sulcus fixation were as follows: three UBM parameters (SS-CP, SS-LS, and CP-LS); refractive error (RF; measured using an autorefractor keratometer [ARK-1a; Nidek, Nagoya, Japan]); axial length (AXL); anterior chamber depth (ACD); lens thickness (LT; measured by partial coherence laser interferometry [IOL master 700; Carl Zeiss Meditec AG, Jena, Germany]); lens position (LP; ACD + 1/2 LT); and relative lens position (RLP; LP/AXL [%]).

Statistical analysis

Data analyses were performed using Statcel—The Useful Add-in Software Forms on Excel—4th ed. (The Publisher OMS Ltd., Tokyo, Japan) and BellCurve for Excel (Social Survey Research Information Co., Ltd.). Age was assessed using an unpaired *t*-test, whereas other data were assessed using Fisher's exact test. The biometric data of the patients were analyzed using an unpaired *t*-test or the Mann–Whitney *U* test. The significance was set at $P < 0.05$. The performance of the UBM parameters was evaluated on the basis of the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Two experienced ophthalmologists (Y.C. and Y.A.) measured the UBM parameters independently in a masked fashion. Inter-observer and intra-observer reproducibility were estimated using the intra-class correlation coefficient (ICC) for the CP-LS parameter. Each observer measured one position three times to estimate the intra-observer reproducibility. The parameters measured by observer A were used for data analysis in this study.

RESULTS

Out of 133 eyes, 18 (13.5%), 50 (37.6%), and 65 (48.9%) eyes were diagnosed with PACS, PAC, and PACG, respectively. Of the 68 eyes with zonular weakness, 1, 37, and 30 eyes were diagnosed with PACS, PAC, and PACG, respectively. Furthermore, out of the 65 eyes without zonular weakness, 30 and 35 eyes were diagnosed with PAC and PACG, respectively, whereas none were diagnosed with PACS. No differences in the prevalence of disease type were observed between the groups. Based on the Emery–Little classification (50 out of 68 eyes with zonular weakness, medical records data), 10 were grade I, 26 were grade II, 11 were grade

III, and 3 were grade IV. Similarly, among 48 out of 65 eyes without zonular weakness, 12 were grade I, 27 were grade II, 7 were grade III, and 2 were grade IV. No differences were observed between the two groups in the number of cases in each cataract grade. LPI or APAC was more prevalent in eyes with zonular weakness than in those without zonular weakness; all five eyes with LPI and 13 out of 14 eyes with APAC demonstrated zonular weakness ($P < 0.05$).

Table 1 shows the characteristics and anatomical parameters of the 68 and 65 eyes with and without zonular weakness, respectively. The eyes with zonular weakness were more myopic but had a shorter AXL, shallower ACD, thicker lens, and forward-positioned lens ($P < 0.05$ for all comparisons performed using the unpaired *t*-test; Table 1). Table 2 shows the comparisons of the UBM parameters between the eyes with and without zonular weakness. SS-CP and CP-LS were longer in eyes with zonular weakness compared with those without zonular weakness ($P < 0.01$; unpaired *t*-test, and Mann–Whitney *U* test, respectively; Table 2). Table 3 shows the characteristics and anatomical parameters of the eight eyes that underwent sulcus fixation of the IOL and 125 eyes that did not. No differences in characteristics were observed between the two groups (Table 3). The eyes that underwent sulcus fixation of the IOL presented with a shallower ACD and thicker lens; the location of the lens was more forward compared with that in the eyes that did not undergo sulcus fixation of the IOL ($P < 0.05$, Mann–Whitney *U* test for ACD and unpaired *t*-test for other parameters; Table 3). The CP-LS was longer in eyes that underwent sulcus fixation of the IOL than in those that did not ($P < 0.01$, unpaired *t*-test; Table 4).

The ROC curves of the parameters used to differentiate the group with zonular weakness from that without zonular weakness are shown in Figure 2, and the AUCs are summarized in Table 5. The AUCs for RF, AXL, ACD, LT, LP, SS-CP, and CP-LS were 0.61, 0.62, 0.72, 0.69, 0.66, 0.62, and 0.64, respectively. The ROC curves of the parameters used to differentiate the group that underwent sulcus fixation of the IOL from the group that did not are shown in Figure 3, and the AUCs are summarized in Table 5. The AUCs for ACD, LT, LP, RLP, and CP-LS were 0.78, 0.71, 0.73, 0.78, and 0.84, respectively. The ideal cutoff values for CP-LS, as determined using Youden's index (= sensitivity − [1 − specificity]), was 1.12 mm (sensitivity, 0.88; specificity, 0.81). The intra-observer ICC of observers A and B was 0.97 and 0.94, respectively. The inter-observer ICC between observers A and B was 0.92.

DISCUSSION

The patent LPI was more prevalent in eyes with zonular weakness than in those without zonular weakness in the present study. This result was in agreement with those of previous studies, which showed that the LPI can induce zonular weakness or crystalline lens dislocation [25, 26]. Furthermore, the APAC was more prevalent in eyes with zonular weakness than in those without zonular weakness, in the present study ($P < 0.05$). Sakabe et al. reported that experimentally induced zonular weakness resulted from an IOP that was ≥8 times the normal value [27]. In patients with a history of acute angle closure attack, Kwon et al. reported a shallower ACD, higher lens vault, and lower hyperopic spherical equivalent in eyes with zonular weakness [28]. Our results were in agreement with those of previous studies [27, 28] because a history of APAC (which indicates acute IOP elevation) was prevalent in eyes with zonular weakness.

In the present study, there was no significant difference in age between patients who presented with zonular weakness and those without zonular weakness in the eyes. By contrast, patients with eyes that underwent sulcus fixation were older (albeit with marginal significance) than those with eyes that did not undergo sulcus fixation; this finding is in line with that of a previous study [29].

Significant differences in CP-LS, measured by UBM, were observed in the present study. Assia et al. reported that the average distance between the anterior zonular attachment and the CP in eyes obtained postmortem was 1.6 ± 0.16 mm, as measured using a caliper [29]. According to Pavlin et al., the UBM signs of zonular abnormality can be expressed as direct and indirect signs [23]. They classified defective (or missing) zonular fibers, increased zonular fiber length, and presence of a zonular remnant as direct signs, whereas increased lenticular sphericity, ciliary body flattening, and increased lens–ciliary body distance were categorized as indirect signs [23]. The present study provides quantitative data for zonular abnormality (elongation of the zonular fiber) in PACD eyes before surgery. This result is consistent with both the direct and indirect signs described by Pavlin et al.

CP-LS exhibited the best performance in distinguishing between eyes that underwent sulcus fixation and those that did not, using a ROC curve with an AUC of 0.84. The cutoff value of 1.12 mm was longer than the normal length of the anterior zonular fibers (1.0 mm), but shorter than the length of the stretched zonular fibers (2.0 mm) as described by Pavlin et al. [23]. The authors reported 18 eyes with zonular abnormality, including pseudoexfoliation, congenital spherophakia, surgical procedure, trauma, and Marfan syndrome; however there was no detailed information about the normal length of the zonular fiber in their article [23]. Only PACD eyes were examined in the present study. Eyes with a zonular abnormality that could be detected before surgery, such as severe phacodonesis, lens subluxation, history of trauma, and pseudoexfoliation were excluded.

In this study, both inter-observer ICC and intra-observer ICC were high in UBM parameter measurement. Tello et al. reported the intra-observer reproducibility is high and inter-observer reproducibility is low in the UBM examination [30]. In our study, there were some landmarks such as CP and LS that were relatively easy to identify, so both intra-observer ICC and inter-observer ICC were high.

This study has several limitations. First, it was a retrospective case–control study targeting patients from a single hospital, which may have led to a selection bias. Second, the number of eyes with zonular weakness was small; and therefore, cases with binocular zonular weakness were also recruited in this study so that sufficient data was available for robust analysis. This may also have led to selection bias. Third, the number of patients who underwent sulcus fixation was small. Fourth, the diagnosis of zonular weakness was subjective because it was based on the intraoperative findings reported by surgeons; thus, it was difficult to classify the severity of zonular weakness. Thus, additional studies including a larger cohort are required to confirm the results of this study.

In conclusion, the results of this study indicate that UBM before surgery is necessary for patients with PACD eyes and coexisting cataracts, particularly for those who have a patent LI and a history of APAC. A longer distance between the CP and the edge of the LS (CP-LS) entailed a more difficult cataract surgery and a more frequent sulcus fixation of the IOL. UBM examination is useful for the detection of zonular weakness before surgery for PACD eyes.

ACKNOWLEDGEMENTS

The authors would like to thank Enago for the English language review.

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Table 1 Patients' characteristics and biometry with or without zonular weakness

	zonular weakness (+)	zonular weakness (-)	*P*-value
No. eyes	68	65	N/A
Age (years)[c]	71.5 ± 13.9	69.0 ± 12.0	0.26[a]
Men / Women	16/52	17/48	0.73[b]
Eye (Right / left)	30/38	32/33	0.55[b]
Refractive error (RF) (diopter)[c]	-0.13 ± 4.83	1.33 ± 2.65	< 0.05[a]
Axial length (AXL) (mm)[c]	22.61 ± 0.91	23.00 ± 0.88	< 0.05[a]
Anterior chamber depth (ACD) (mm)[c]	2.32 ± 0.43	2.61 ± 0.34	< 0.01[a]
Lens thickness (LT) (mm)[c]	5.14 ± 0.50	5.00 ± 0.39	< 0.01[a]
Lens position (LP) (mm)[c]	4.89 ± 0.36	5.06 ± 0.25	< 0.01[a]
Relative lens position (RLP) (%)[c]	21.68 ± 1.73	22.02 ± 1.08	0.17[a]

[a]Unpaired t test

[b]Fisher's exact test

[c]Values are expressed as the mean ± standard deviation

Table 2 The UBM parameters in comparison between the eyes with and without zonular weakness

	zonular weakness (+)	zonular weakness (-)	*P*-value
SS[a]-CP (mm)[b]	1.31 ± 0.17	1.23 ± 0.11	< 0.01[e]
SS-LS (mm)[c]	1.33 ± 0.22	1.29 ± 0.20	0.28[e]
CP-LS (mm)[d]	0.77 ± 0.72	0.32 ± 0.37	< 0.01[f]

[a] Scleral Spur

[b] The length of perpendicular line drawn from the point ciliary process (CP) to the base line

[c] The length of perpendicular line drawn from the point lens surface (LS) to the baseline

[d] The length between the CP and LS

[e] Unpaired t test

[f] Mann-Whitney's U test

Table 3 Patients' characteristics and biometry of eyes underwent or not sulcus fixation of IOL

	sulcus fixation (+)	sulcus fixation (-)	*P*-value
No. eyes	8	125	-
Age (years)[d]	78.8 ± 12.5	69.7 ± 12.9	0.06[a]
Men / Women	4/4	29/96	0.09[b]
Eye (Right / left)	3/5	59/66	0.59[b]
Refractive error (RF) (diopter)[d]	0.75 ± 6.31	0.61 ± 3.78	0.93[a]
Axial length (AXL) (mm)[d]	23.25 ± 1.07	22.77 ± 0.90	0.14[a]
Anterior chamber depth (ACD) (mm)[d]	2.00 ± 0.62	2.50 ± 0.38	< 0.01[c]
Lens thickness (LT) (mm)[d]	5.33 ± 0.46	4.98 ± 0.48	< 0.05[a]
Lens position (LP) (mm)[d]	4.65 ± 0.47	5.00 ± 0.30	< 0.01[a]
Relative lens position (RLP) (%)[d]	20.10 ± 2.71	21.96 ± 1.26	< 0.01[a]

[a]Unpaired t test

[b]Fisher’s exact test

[c]Mann-Whitney's U test

[d]Values are expressed as the mean ± standard deviation

Table 4 The UBM parameters in comparison between the eyes underwent the sulcus fixation of IOL and the eyes not underwent the sulcus fixation of IOL

	sulcus fixation (+)	sulcus fixation (-)	*P*-value[e]
SS[a]-CP (mm)[b]	1.43 ± 0.23	1.26 ± 0.14	0.08
SS-LS (mm)[c]	1.37 ± 0.19	1.31 ± 0.21	0.45
CP-LS (mm)[d]	1.31 ± 0.57	0.51 ± 0.59	< 0.01

[a] Scleral Spur

[b] The length of perpendicular line drawn from the point ciliary process (CP) to the base line

[c] The length of perpendicular line drawn from the point lens surface (LS) to the baseline

[d] The length between the CP and LS

[d]Unpaired t test

Table 5 Area under the curve (AUC) of parameters in current study

	Zonular weakness	Sulcus fixation
Refractive error (RF)	0.61	0.78
Axial length (AXL)	0.62	-
Anterior chamber depth (ACD)	0.72	-
Lens thickness (LT)	0.69	0.71
Lens position (LP)	0.66	0.73
Relative lens position (RLP)	-	0.78
parameter SS[a]-CP[b]	0.62	-
parameter CP-LS[c]	0.64	0.84

[a] Scleral Spur

[b] The length of perpendicular line drawn from the point ciliary process (CP) to the base line

[c] The length between the CP and the lens surface (LS)

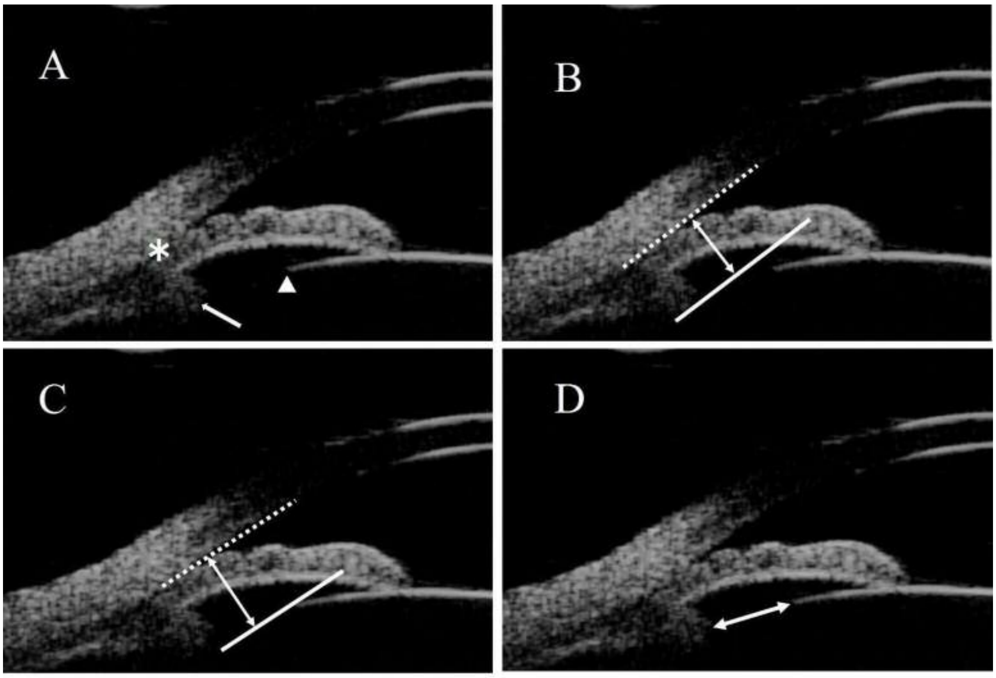

Fig.1
(a) On ultrasound biomicroscopy (UBM) images, scleral spur (SS; asterisk), top of the ciliary process (CP; arrow), and the edge of the lens surface (LS; arrow head) were identified. (b) The SS-CP Parameter was defined as the length of perpendicular line drawn from the point CP to the base line (dashed line). (c) The SS-LS Parameter was defined as the length of perpendicular line drawn from the point LS to the baseline (dashed line). (d) The CP-LS Parameter was defined as the length between the CP and the LS (double-headed arrow).

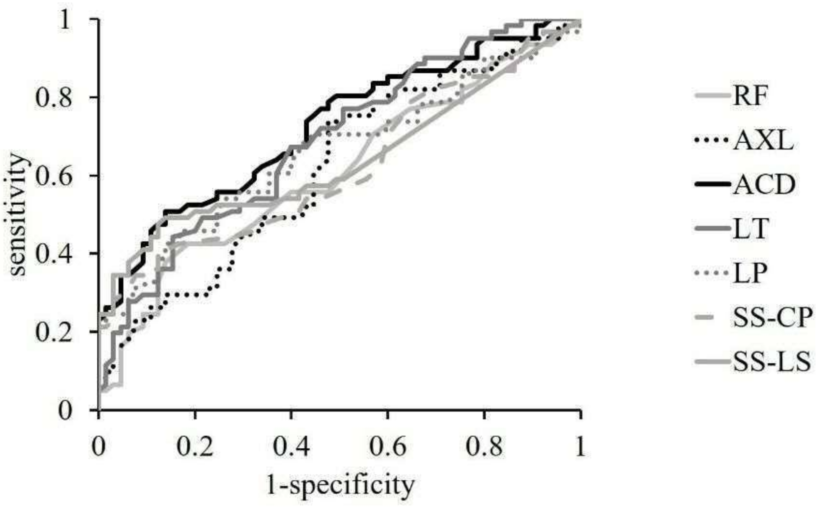

Fig.2
The receiver operating characteristic (ROC) curves and the area under the curves (AUCs) of the parameters for differentiating the group with zonular weakness and the group without zonular weakness. AUCs for refractive error (RF), axial length (AXL), anterior chamber depth (ACD), lens thickness (LT), lens position (LP), SS-CP parameter, and CP-LS parameter were 0.61, 0.62, 0.72, 0.69, 0.66, 0.62, and 0.64, respectively.

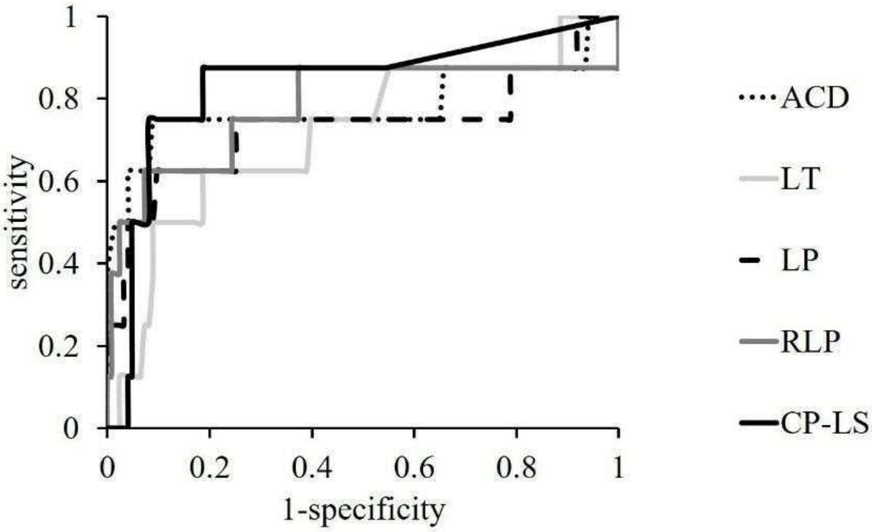

Fig.3

The ROC curves and AUCs of the parameters for differentiating the group underwent the sulcus fixation of IOL and the group not underwent the sulcus fixation of IOL. AUCs for ACD, LT, LP, relative lens position (RLP), and CP-LS parameter were 0.78, 0.71, 0.73, 0.78, and 0.84, respectively.